

Organizational Pattern of a complete chapter As far as possible this structure has been followed in each chapter

CHAPTER 5

ADRENALS

PRECLINICAL

SECTION	PAGE
39 PRELIMINARY	643
I History	643
II Anatomy	645
III Embryology	646
IV Congenital Anomalies	647
V Histology	647
VI Functions	648
VII Chemistry	656
VIII Bio assay	658
IX Pathology	661
X Classification	663
XI Chief Clinical Findings of Hyposecretion	664
XII Chief Clinical Findings of Hypersecretion	664
XIII Examination of the Patient	665

CLINICAL

40 ADDISON'S DISEASE	690
I Definition	690
II Appearance	690
III Age	690
IV Sex	690
V Mental Deviations	690
VI Physical Status	690
VII Laboratory Data	692
VIII Roentgenographic Findings	694
IX Etiology	695
X Pathology	695
XI Pathologic Physiology	697
XII Symptomatology	698
XIII Diagnosis	699
XIV Differential Diagnosis	700
XV Complications, Sequelae or Associated Diseases	701
XVI Treatment	702
XVII Prognosis	706
XVIII Causes of Death	706
41 WATERHOUSE FRIDERICHSEN SYNDROME	716
I Definition	716
II Appearance	716
III Age	716
IV Sex	716
V Mental Deviations	716
VI Physical Status	716
VII Laboratory Data	716
VIII Etiology	717
IX Pathology	717
X Symptomatology	717
XI Diagnosis	717
XII Treatment	718
XIII Prognosis	718
XIV Causes of Death	718

SECTION	PAGE
42 THE ANDRENOGENITAL SYNDROMES	719
I Definition	719
II Appearance	719
III Age	719
IV Sex	719
V Mental Deviations	719
VI Physical Status	721
VII Laboratory Data	722
VIII Roentgenographic Findings	722
IX Etiology	723
X Pathology	723
XI Pathologic Physiology	724
XII Symptomatology	724
XIII Diagnosis	725
XIV Differential Diagnosis	726
XV Complications Sequelae and Associated Diseases	726
XVI Treatment	727
XVII Prognosis	727
XVIII Causes of Death	727
43 FEMINIZING SYNDROME DUE TO MALIGNANT ADRENAL CORTICAL TUMOR	733
I Definition	733
II Appearance	733
III Age	733
IV Mental Deviations	733
V Physical Status	733
VI Laboratory Data	733
VII Roentgenographic Findings	733
VIII Etiology	734
IX Pathology	734
X Pathologic Physiology	734
XI Symptomatology	734
XII Diagnosis	734
XIII Differential Diagnosis	734
XIV Complications	734
XV Treatment	734
XVI Prognosis	735
XVII Causes of Death	735
44 HYPERFUNCTION OF ADRENAL MEDULLARY OR OTHER CHROMAFFIN TISSUE DUE TO PHEOCHROMOCYTOMA	737
I Definition	737
II Appearance	737
III Age	737
IV Sex	737
V Mental Deviations	737
VI Physical Status	737
VII Laboratory Data	739
VIII Roentgenographic Findings	740
IX Etiology	741
X Pathology	741
XI Pathologic Physiology	742
XII Symptomatology	742
XIII Diagnosis	743
XIV Differential Diagnosis	744
XV Complications Sequelae and Associated Diseases	744
XVI Treatment	745
XVII Prognosis	745
XVIII Causes of Death	745

CLINICAL
ENDOCRINOLOGY

VOLUME ONE



PURPLISH STRIAE—A SIGN OF HYPERADRENAL CORTICALISM (CUSHING'S SYNDROME) Lump noted in neck which proved to be a carcinoma simplex probably of thyroid origin. Chest roentgenograms revealed a right substernal and mediastinal tumor displacing the trachea forward and causing paralysis of the right laryngeal nerve. Roentgen therapy was not effective. As the tumor increased in size the patient gained 20 lbs. in 3 months, developed marked striae and a moon face. Complete loss of libido. On one occasion he had coliclike abdominal pain with dysuria, question of possible renal stone. BP 130/100. Postmortem revealed normal pituitary and adrenal glands. The tumor probably spread from the right lobe of the thyroid, infiltrating the mediastinum with metastases to the lungs and other tissues.

CLINICAL ENDOCRINOLOGY

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TWO VOLUMES

482 Figures 146 Charts 1 Color Plate

VOLUME ONE



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DEDICATION

To Dorothy my wife and to
Lewis Gretchen Ben Katherine
my children

LEWIS M HURXTHAL

DEDICATION

To my Mother
and to the memory of my Father

NATALIJA MUSULIN

Preface

The present work not only embodies many years of individual clinical experience on the part of the authors, but also a diligent searching and co-ordination of world literature in Endocrinology. This branch of medicine has become one of the very important and most rapidly expanding fields with considerable potentialities and has created a new type of therapeutic management. Since an overabundance of papers is being published on this subject we have made every effort to provide a permanent framework within which essential additional data can be organized.

The reader will note at once that the entire text is in outline form. The twenty-five chapters include the physiologic functions and diseases of all the endocrine glands; those organs that have both endocrine and nonendocrine activities; the multiple interrelated bodily and metabolic significance of these both normal and abnormal; and the clinical application of hormonal preparations.

The chapters dealing with the principal glands have been subdivided into preclinical and clinical parts and where feasible, this arrangement has been utilized throughout the book. There is further division into smaller sections as a suitable means of dealing with the wide scope of this field. Each subdivision has a definite pattern (see front end leaves of either volume) which has been followed with as much consistency as possible. The Roman numerals provide the basic scheme for presenting the material; some deviation has occurred for the sake of compactness and more facile adaptation. The end leaves in the back of each volume contain the laboratory data to be used as reference for average normal findings.

Our policy has been to adhere to certain sequences whenever applicable: for example normal, decrease or hypofunction, and then increase or hyperfunction. The glands are discussed according to their position in the body, likewise the order of children, males and females and that of carbohydrate, fat and

protein are fairly uniform. Similar analogies will be apprehended as one becomes familiar with the structure of the whole book.

Multiple cross references will be found; the exact location of each is keyed according to the section number and outline pattern, thus offering quick access to the material to be correlated. The running head (dictionary style) carries these numbers and letters for this purpose.

Thirty-nine protocols are presented as symbolic examples of the clinical syndromes. Case histories have a section number (Arabic) and a protocol number (Roman) e.g., Protocol 37, XXI. The style is the customary procedure for history taking and follows the main outline of the text.

The bibliographies while extensive have been critically chosen and will be helpful as adequate and basic guides to additional reading and exploration. The references appear at the end of each chapter after the protocols and are arranged in alphabetic order for every individual section. However, in the preclinical division (with a few exceptions), they coincide with the Roman numerals as a matter of convenience and simplicity. Superior figures in the text indicate the references.

The illustrations and the charts have been selected to demonstrate the best clinical features or characteristics, the results of therapy, comparison and contrasts for the different endocrine problems. These have been grouped at the end of each section as an advantageous way of comparing similar cases and those of other clinical entities.

The authors are indebted to Dr. Frank H. Lahey for his permission to use the cases of the Lahey Clinic. We are also grateful to the other staff members who obligingly contributed their suggestions. The authors especially wish to thank Dr. A. Seymour Parker for his collaboration in preparing the chapter on Sterility.

We acknowledge the great contribution

made by numerous investigators to medical literature, without which this work could not have been compiled

Some of the former Fellows in Internal Medicine aided us by their stimulating curiosity and questioning We wish to express our appreciation to them and especially for the assistance of the following Dr James H Coll (Duluth Minn), in preparing the parathyroid chapter Dr Omar Z Younghusband (Ontario Canada), for his analysis of our cases in the summary on chromophobe tumors Dr John M Elliott (San Francisco Calif) for his service on the sections on the pineal the thymus and clinical use of adrenocorticotropin, Dr Kenneth R Kaess (Waterbury, Conn) in revising the part on radioactive iodine therapy for thyroid disease

Dr Shields Warren and Dr William Messner, of the New England Deaconess Hospital, kindly made the pathologic reports We were fortunate in having Dr O J Pollak (Milford and Beebe Hospitals, Dover and Lewes Delaware) review the slides of the testicular biopsies We are most grateful for the above assistance

The Schering Corporation, Ayerst, McKenna and Harrison, Limited, Ciba Pharmaceutical Products, Incorporated, and The Upjohn Company generously supplied the endocrine preparations used in many of the cases reported herein for their contributions we express our appreciation

LEWIS M HURXTHAL
NATALIJA MUSULIN

Contents

VOLUME ONE

CHAPTER 1

NORMAL GROWTH AND DEVELOPMENT

SECTION

- | | | |
|---|-------------------------------|---|
| 1 | Normal Growth and Development | 3 |
|---|-------------------------------|---|

CHAPTER 2

PITUITARY

PRECLINICAL

- | | | |
|---|-------------|----|
| 2 | Preliminary | 31 |
|---|-------------|----|

CLINICAL

- | | | |
|----|----------------------------------|-----|
| 3 | Prepuberal Hypopituitarism | 114 |
| 4 | Postpuberal Hypopituitarism | 140 |
| 5 | Simmonds' Disease | 152 |
| 6 | Pituitary Myxedema | 174 |
| 7 | Pituitary Adrenal Insufficiency | 177 |
| 8 | Diabetes Insipidus | 184 |
| 9 | Gigantism | 194 |
| 10 | Acromegaly | 216 |
| 11 | Cushing's Syndrome (Basophilism) | 247 |
| 12 | Chromophobe Tumors | 278 |
| 13 | Summary of Tumors | 281 |

CHAPTER 3

THYROID

PRECLINICAL

- | | | |
|----|-------------|-----|
| 14 | Preliminary | 295 |
|----|-------------|-----|

CLINICAL

- | | | |
|----|--|-----|
| 15 | Endemic Goiter | 348 |
| 16 | Colloid Goiter | 353 |
| 17 | Nodular (Multiple) Goiter | 356 |
| 18 | Intrathoracic Goiter | 359 |
| 19 | Thyroiditis—Acute Nonsuppurative and Suppurative | 368 |
| 20 | Chronic Nonspecific Thyroiditis | 371 |
| 21 | Riedel's Struma | 373 |
| 22 | Hashimoto's Struma | 376 |
| 23 | Infectious Granulomata | 380 |
| 24 | Cretinism | 381 |

CLINICAL (Continued)

SECTION

25	Myxedema	406
26	Hyperthyroidism	431
27	Persistent Hyperthyroidism	491
28	Recurrent Hyperthyroidism	493
29	Apathetic Hyperthyroidism	498
30	The Thyrocardiac Patient	500
31	Hyperthyroidism and Diabetes Mellitus	513
32	Hyperthyroidism and Pregnancy	515
33	Exophthalmic Syndrome	518
34	Factitious Hyperthyroidism	527
35	Tumors	533

CHAPTER 4

PARATHYROIDIS

PRECLINICAL

36	Preliminary	555
----	-------------	-----

CLINICAL

37	Primary Hypoparathyroidism	576
38	Primary Hyperparathyroidism	600

CHAPTER 5

ADRENALS

PRECLINICAL

39	Preliminary	643
----	-------------	-----

CLINICAL

40	Addison's Disease	690
41	Waterhouse Friderichsen Syndrome	716
42	The Adrenogenital Syndromes	719
43	Feminizing Syndrome Due to Malignant Adrenal Cortical Tumor	733
44	Hyperfunction of Adrenal Medullary or Other Chromaffin Tissue Due to Pheochromocytoma	737

VOLUME TWO

CHAPTER 6

TESTES

PRECLINICAL

45	Preliminary	753
----	-------------	-----

CLINICAL

46	Cryptorchidism	795
----	----------------	-----

TYPES OF MALE HYPOGONADISM

47	Group I Prepuberal Eunuchism and Eunuchoidism	805
48	Group II Prepuberal Degenerative Castration	837

CLINICAL (Continued)

SECTION		
49	Group III Midpuberal Hypogonadism or Arrest	838
50	Group IV Postpuberal Eunuchism	841
51	Group V Seminiferous Tubular Hypofunction	846
52	Group VI Turner's Syndrome	857
53	Climacteric	861
54	Tumors	863
55	Benign Prostatic Hypertrophy	876
56	Cancer of the Prostate Gland	881

CHAPTER 7
OVARIES

PRECLINICAL

57	Preliminary	891
----	-------------	-----

CLINICAL

58	Normal Menstruation	941
59	Menopause	948
60	Totemias of Pregnancy	955
61	Disorders of Menstruation	963
62	Endometriosis	988
63	Vulvovaginitis	998
64	Ovarian Short Stature Syndrome	1001
65	Female Eunuchoidism or Eunuchism	1016
66	Nonendocrine Tumors	1033
67	Nonneoplastic Cysts	1040
68	Miscellaneous Tumors and Diseases	1047
69	Carcinoma	1051
70	Granulosa Cell Tumor	1055
71	Theca Cell Tumor	1061
72	Luteoma	1064
73	Arrhenoblastoma	1066
74	Adrenal like Tumor	1070
75	Dysgerminoma	1074
76	Gynandroblastoma	1077
77	Chorionepithelioma	1078
78	Struma Ovarii	1082
79	Brenner's Tumor	1084

CHAPTER 8
HERMAPHRODISM

80	Pseudohermaphrodisism	1089
81	True Hermaphrodisism	1095

CHAPTER 9
STERILITY

82	Sterility	1099
----	-----------	------

CHAPTER 10

PANCREAS

PRECLINICAL

SECTION

83 Preliminary	1165
----------------	------

CLINICAL

84 Diabetes Mellitus	1188
85 Hyperinsulinism	1241

CHAPTER 11

PINEAL

PRECLINICAL

86 Preliminary	1255
----------------	------

CLINICAL

87 Tumor Syndrome	1259
-------------------	------

CHAPTER 12

HYPOTHALAMUS

88 Hypothalamus	1267
-----------------	------

CHAPTER 13

THYMUS

PRECLINICAL

89 Preliminary	1279
----------------	------

CLINICAL

90 Myasthenia Gravis	1286
91 Status Thymicolymphaticus	1290

CHAPTER 14

DWARFISM

PRECLINICAL

92 Preliminary and Chief Characteristics	1295
--	------

CLINICAL

93 Progeria	1320
94 Mongoloidism	1324
95 Laurence Moon Biedl Syndrome	1333

CHAPTER 15

HAIR GROWTH IN RELATION TO THE ENDOCRINE GLANDS

96 Hair Growth in Relation to the Endocrine Glands	1341
--	------

CHAPTER 16

OBESITY

SECTION

97 Obesity	1347
------------	------

CHAPTER 17

ENDOCRINE ASPECTS OF HYPERTENSION

98 Endocrine Aspects of Hypertension	1357
--------------------------------------	------

CHAPTER 18

THE GENERAL ADAPTATION SYNDROME

99 The General Adaptation Syndrome	1365
------------------------------------	------

CHAPTER 19

ENDOCRINE ROLE OF THE LIVER

100 Endocrine Role of the Liver	1373
---------------------------------	------

CHAPTER 20

MAMMARY GLANDS

101 General	1385
102 Gynecomastia	1402

CHAPTER 21

METABOLISM

103 Metabolism	1413
----------------	------

CHAPTER 22

GASTRO INTESTINAL HORMONES

104 Gastro-intestinal Hormones	1477
--------------------------------	------

CHAPTER 23

ANTIHORMONES

105 Antihormones	1481
------------------	------

CHAPTER 24

PITUITARY AND CHORIONIC HORMONES

106 Clinical Bio assay and Uses	1489
---------------------------------	------

CHAPTER 25

STEROID COMPOUNDS

107 Description Clinical Bio assay and Uses	1511
---	------

Index	1539
-------	------

CLINICAL
ENDOCRINOLOGY

VOLUME ONE

CHAPTER 1

Normal Growth and Development

Section 1

- I DEFINITION
 - II GENERAL SUMMARY OF FACTORS TO BE EVALUATED
 - III INFLUENCING FACTORS
 - IV STAGES
 - V METHODS OF MENSURATION
 - VI VARIATIONS OF NORMAL PUBESCENCE
-

SECTION 1

NORMAL GROWTH AND DEVELOPMENT

I DEFINITION

NORMAL STANDARD—A state of normal growth and development exists if after the proper integration of certain essentials, the result is within the norm for any given chronologic age

II GENERAL SUMMARY OF FACTORS TO BE EVALUATED

A BASIC OBSERVATIONS

- 1 Mentality
- 2 Weight
- 3 Height
- 4 Sexual development
- 5 Skeletal maturation

B RELATIONSHIP TO CHRONOLOGIC AGE—Comparison of the above with chronologic age gives the various ages (see below)

C SPECIFIC DATA TO BE MEASURED OR ASSESSED

- 1 Psychometry
 - a Nursing ability
 - b Age (variable) of

	WEEKS
(1) Perception	6 12
(2) Sitting	24 30
(3) Crawling	35 45
(4) Standing	52
(5) Thumb to index finger co ordination	52
(6) Walking	56 72

YEARS

- | | |
|--------------------------------------|-----|
| (7) Drawing a recognizable
object | 4 5 |
| (8) Copying figures | 5 |
| (9) Reading | 5 6 |
| (10) Writing | 5 7 |
- Intelligence quotient (IQ)—the general intelligence of a person expressed quantitatively by a total score in terms of years and months which has been determined in a graded series of tests

d Social demeanor

e Sexual behavior

f Emotional response

2 Weight (see I V B)

3 Linear measurements (see I V C)

a Height

b Length of extremities

(1) Upper (span)

(2) Lower

4 Teeth (see Tables 1 and 2)

a Time of eruption

b Stage of development by roentgen studies

5 Sexual maturation

a Genitalia (see I V F)

b Hair growth

c Breast size

6 Osseous roentgenography

a Skull

(1) Sutures (see Table 3)

(2) Sella turcica (see 2 V C)

(3) Sinuses

(4) Teeth

b Bone age (see I V D 103 V B)

(1) Epiphyseal development

(2) Carpal status

c Long bones

(1) Width

(2) Length

d Pelvic aperture (shape)

■ Texture

TABLE 1 DECIDUOUS DENTITION °

TOOTH	CALCIFICATION BEGINS IN UTERO MONTHS	ERUPTION MONTHS
Incisor 1	5	6 8
Incisor 2	5	8 10
Cuspid	6	16 20
Molar 1	5	12 16
Molar 2	6	20 30

TABLE 2 PERMANENT DENTITION *

TOOTH	UPPER JAW		LOWER JAW	
	Calcification Begins Months	Eruption Years	Calcification Begins Months	Eruption Years
Incisor 1	3-4	7-8	3-4	6-7
Incisor 2	12	8-9	3-4	7-8
Cuspid	4-5	11-12	4-5	9-10
	Years		Years	
Bicuspid 1	1½-1¾	10-11	1¾-2	10-11
Bicuspid 2	2-2¼	11-12	2¼-2½	11-12
Molar 1	Birth	6-7	Birth	6-7
Molar 2	2½-3	12-13	2½-3	11-13
Molar 3	7-9	17-21	8-10	17-21

TABLE 3 CLOSURE OF FONTANELS AND SUTURE LINES^{3*}

FONTANELS	APPROXIMATE AGE FOR CLOSURE
Posterior (occipital)	<div> <div>Prenatal—during last 2 months or</div> <div>Postnatal—by first 2 months</div> </div>
Anterolateral (sphenoidal paired)	During first 3 months
Anterior (frontal)	During first half of second year (almost complete)
Posterolateral (mastoid paired)	During second year
SUTURES	
Mendosal (between upper and lower portions of squamous bone paired)	By several weeks after birth
Frontal (metopic)	Starts at second year complete during third year (may persist)
Spheno occipital synchondrosis	Begins around puberty or may persist until twentieth year
Great—coronal lambdoidal sagittal	Onset about thirtieth year

* Not reliable for estimation of developmental age of skull

D EXCRETORY SECRETORY AND OTHER OBTAINABLE EVIDENCE

1 Perspiration

- Absence
- Excess

2 Testicular function

- Examination of seminal fluid (see 82 VII D)

b Biopsy (see 45 VIII B 4 b)

- Leydig cells
- State of spermatogenesis

3 Ovarian function

- Menstrual cycle (see 58)
- Endometrial biopsy (see 82 IV B 1)
- Vaginal smear (see 57 VIII E 2)

4 Urinary and fecal (quantitative) excretion studies

a Urinary

- Nitrogen
- Creatine
- Creatinine
- Potassium
- Calcium
- Phosphorus

b Fecal

- Minerals
- Fats

c These are rarely indicated in clinical practice, except in special investigations

d Of little value unless done in organized metabolic services

5 Complete blood count

6 Blood chemical analyses

a Sugar

b Protein

c Cholesterol

d Phosphorus (inorganic)

- Child—4.5 to 6.5 mg %
- Adult—3.0 to 4.5 mg %

e Phosphatase (alkaline)—in Bodansky units

- Child—5 to 14
- Adult—1.4 to 4

- 7 Oxygen consumption (basal metabolic rate or BMR)
- 8 Hormones (urinary assay—Charts 1-3)
 - a Gonadotropins (follicle stimulating hormone (FSH) essentially—luteinizing hormone (LH) is difficult to determine and probably of minimal quantities)
 - b Estrogens
 - c Pregnenolone
 - d 17 ketosteroids
 - e 11 oxysteroids

- d Emotion (alarm reaction)
- e Mechanical (i.e., cord anomalies, placental defects)
- f Age of pregnancy

D POSTNATAL

- 1 Inherent capacity of cells of organism to grow, but this is difficult to evaluate and may be genetically predetermined²

2 Hormones for growth

- a Pituitary growth
 - (1) Active up to 17 or 19 years (possibly to 25)
 - (2) Minimal or expended after that

- b Thyroid—an essential synergist for complete function of pituitary growth hormone

- c Parathyroid—less vital in growth process than other hormones

d Adrenocortical

- (1) Androgenic (A) factors may limit linear growth by causing epiphyseal closure in females
- (2) Pituitary growth hormone may be inhibited at adolescence

e Testicular (testosterone)

- (1) Chief factor probably (plus above) for epiphyseal closure in males
- (2) Pituitary growth hormone may be inhibited at adolescence
- (3) Better tissue builder than estrogen or adrenocortical A hormones therefore greater muscular and skeletal development in males

f Estrogen

- (1) Pituitary may be stimulated to produce adrenocortical A hormones before or at menarche
- (2) When secreted in larger amounts it may be chief inhibitor of pituitary growth hormone at adolescence

- g Insulin—necessary ingredient of tissue synthesis and hence growth

3 Nutritional status is affected by the intake or absorption of

- a Certain foods
- b Minerals
- c Vitamins

III INFLUENCING FACTORS

A HEREDOFAMILIAL

- 1 Congenital endocrine disorders
- 2 Intelligence
- 3 Weight
- 4 Height
- 5 Bodily configuration
- 6 Hair growth and distribution
- 7 Puberty (age of pubescence)

B CONGENITAL

- 1 Defects may be responsible for
 - a Familial (pituitary?) dwarfism
 - b Thyroplasia
 - c Adrenogenital syndrome
 - d Eunuchoidism
 - e Germinal epithelial agenesis
 - f Pseudohermaphroditism
 - g Laurence-Moon Biedl syndrome
 - h Mongolism
 - i Cerebral malformation
- 2 Altered capacity of organ or organs for
 - a Growth
 - b Development

C PRENATAL (possible or probable factors)

- 1 Paternal
 - a Endocrine status
 - b Chronic intoxications (i.e. alcoholism, chemicals)
 - c Hereditary characteristics
- 2 Maternal
 - a As for paternal
 - b Intake and absorption of proper adequate
 - (1) Food
 - (2) Minerals
 - (3) Vitamins
 - c Infectious disease (i.e. rubella)

4 Damaging causes

- a Infection
- b Trauma if serious
- c Emotion
- d Irradiation
- e Other abnormalities
 - (1) Cerebral
 - (2) Pulmonary
 - (3) Cardiovascular
 - (4) Renal
 - (5) Malignant tumors may compete for body nourishment

IV STAGES^{6, 9, 10}

1 GENERAL (see Charts 8, 9 Figs 1, 2)

- 1 The stages of development have been divided into groups as shown in Table 4
- 2 Knowledge of these findings is important in differentiating the normal from the abnormal (see I IV and VI)
- 3 These groups do not always correspond to chronologic age, but are based chiefly on
 - a Height
 - b Skeletal development

TABLE 4 STAGES OF MASCULINE DEVELOPMENT¹⁹

	GROUP 1 PREPUBESCENCE	GROUP 2 INTERMEDIATE PREPUBESCENCE AND PUBESCENCE	GROUP 3 PUBESCENCE	GROUP 4 ADOLESCENCE	GROUP 5 POST ADOLESCENCE	GROUP 6 ADULTHOOD (AFTER 25)
Voice	No change	None or slight change	None or slight change	Changing or changed	Changed	Adult
Breasts	No change	None to slight	May be prominent	Subsided	Absent	Absent
Hair						
Head	Normal	Normal	Normal	Normal	May begin receding	Increased recession
Facial	Absent	Absent	Light slightly pigmented on upper lip	Light beard and mustache	Adult growth	Adult growth
Aural	Absent	Absent	Absent	Absent	Absent	Grows about age 35
Nasal	Absent	Absent	Absent	Absent	Absent	May appear eyebrows may become more bushy
Axillary and pubic	Absent	Slightly pigmented	Sparse but pigmented	Good growth beginning male escutcheon	Adult growth	Adult growth
Body	Absent	None other than down	Few pigmented	Some may be pigmented	Near adult type	May increase
Penis length in cm	3.8	4.5-12	8-15	9-15	10.5-18	10.5-18
Testicular volume in cc	0.3-1.5	4-8	2-20	6-20	8-25	8-25
Prostate	Flat or small	Flat or small	Flat or small	Near adult size	Adult	Adult
	<i>Per</i> <i>Years</i> <i>Cent</i>	<i>Per</i> <i>Years</i> <i>Cent</i>	<i>Per</i> <i>Years</i> <i>Cent</i>	<i>Per</i> <i>Years</i> <i>Cent</i>	<i>Per</i> <i>Years</i> <i>Cent</i>	<i>Per</i> <i>Years</i> <i>Cent</i>
Distribution by chronologic age	1-11 76	10 2	12 10	13 8	15 7	
	12 44	11 12	13 21	14 27	16 20	
	13 15	12 22	14 26	15 53	17 51	
	14 6	13 28	15 22	16 59	18 63	
		14 20.5	16 11	17 39	19 74	
		15 9	17 7	18 30	20-21 83	
		16 5	18 7	19 26	22-25 100	
		17 1.5		20 17		

- Sexual maturation
- 4 The sum total of these variants (a, b, c above as well as others) has been termed maturity or 'somatic age'
- 5 Final maturity or somatic age
 - a Linear growth has ceased
 - b Skeleton is fully developed
 - c Chronologic age of 25 (average)

V METHODS OF MENSURATION

A MENTAL AGE ¹¹

- 1 Special methods for evaluation are not discussed herein
- 2 Reading age
 - a Spurts in
 - (1) Boys at 10 to 11 years
 - (2) Girls at 9 to 10 years
 - b Late menarche may cause a delay
 - c Family accomplishments are important here
- 3 Achievement is only partially dependent on learning processes
 - a Forcing educational methods is inadvisable
 - b Pacing instruction is better because a child rejects what he is not ready to absorb
 - c Expectancy of accomplishments is conditioned by
 - (1) Sex
 - (2) Total maturity (i.e. summation of all 'ages')
 - (3) Familial trends
- 4 Total growth stability i.e. physical and mental is not easily altered

II WEIGHT

- 1 Check preferably
 - a On arising
 - b After voiding
 - Before eating
- 2 Comments
 - a Maintenance of a constant weight in child is equivalent to a loss unless growth has also stopped
 - b Distribution of fat is not significant except possibly in Cushing's syndrome

C HEIGHT AND EXTREMITIES

- 1 Stature
 - a Measure without shoes
 - b Check at same time of day
 - (1) Greater height is found in morning

(2) Afternoon height may decrease by $\frac{1}{2}$ in if individual has been standing all day

(3) A tall person shows a greater difference in morning and afternoon heights and/or with length of time in bed

c Record height at full inspiration and deep expiration

(1) From $\frac{1}{4}$ to $\frac{1}{2}$ in difference may be noted

(2) Repeat observation for confirmation

d Heightmeter with a rigid horizontal and sliding arm is preferred for measurements

■ Last growth rate may be estimated by inspection of school records

f Factors altering measurement

(1) Decrease—weight loss

(2) Increase

(a) Very erect posture

(b) Deep inspiration

(c) Bed rest

2 Span

a Distance between tips of middle fingers with arms outstretched horizontally

b An abnormal increase is not evident until after age of 12

3 Lower extremities are measured from the top of symphysis pubis to floor

4 Feet and hands

a Growth is based on measurements of first and fifth metacarpal or metatarsal bones

b In boys—estimations are of no practical importance

c In girls—these bones stop growing at

- (1) Age 15, if menarche occurs before 12 years

(2) Age 16 or 17 if menarche starts after 13 years

5 Height age—find age on 50 percentile curve (see Charts 5, 8 or 9) to which observed height of subject corresponds

6 Final height (see Charts 4 7)

a Short remain short

b Tall stay tall

c Estimation from Burgess charts (see Charts 145 and 146) but is modified by age of pubescence

- d Prediction may vary from all known growth charts
- (1) Tall children especially
 - (2) When somatic age appears constant with chronologic age
- D BONE AGE**
- 1 Roentgenograms of
 - a Skull for closure of sutures
 - b Hands and wrists
 - c Iliac crests if radial epiphyses are closed
 - d Other epiphyses if desired
 - 2 Estimation
 - a Hands and wrists—comparison with
 - (1) Todd's standards⁴ (see Fig 19)
 - (2) Ossification index of Leonard¹ (see Fig 18)
 - b Iliac crests
 - c Clavicles
 - d 'Ossification sums'⁴ are not practical for routine use
 - 3 Comments
 - a Normal variation—1 year
 - b Abnormal range—2 years or more
 - Advanced bone age, 1 to 2 years—
with greater than average height heralds early onset of puberty
 - d Prediction of final height (see Charts 145 and 146)
 - (1) Useful when bone age is abnormal in children who are
 - (a) Apparently normal and with beginning pubescence
 - (b) Sexually precocious
 - (2) Mark observed height of subject opposite chronologic age which will determine percentile curve (A)
 - (3) Substituting bone age for chronologic age find point where corresponding perpendicular line crosses percentile curve (A above)
 - (4) Read to left of chart for height corresponding to bone age
 - (5) Subtract bone age height from final height on same percentile curve (18 years for girls and 19 years for boys)
 - (6) Add difference to observed height the sum of which may prove to be final height
- (7) If observed height falls beyond curves of chart, suitable interpolation may be made
 - (8) Example
 - (a) Boy with beginning pubescence—chronologic age 9, height 54 in, bone age 12
 - (b) Point falls on 90 percentile curve
 - (c) Height for bone age on this curve—60 in
 - (d) Final height on same curve—71 in
 - (e) 71 minus 60 in equals 11 in
 - (f) Observed height of 54 in plus 11 in (difference of above) equals 65 in for final height
 - (9) Comments on variations in normal growth rate
 - (a) Decreased by
 - [1] Illness
 - [2] Serious injury
 - [3] Food deficiencies (including avitaminosis)
 - (b) Increased
 - [1] In taller or obese children
 - [2] With earlier onset of puberty (bone age may be so advanced that growth ends sooner)

TABLE 5 USEFUL DATA FOR ESTIMATING BONE AGE AFTER CLOSURE OF RADIAL EPIPHYSES¹⁰

BONE	SEX	APPEARANCE OF OSSIFICATION OR CALCIFICATION YEARS	TIME OF EPIPHYSEAL CLOSURE YEARS
Iliac crests	Male	18 20	21 23
	Female	17 19	21 22
Medial end of clavicles	Male	19 20	23 24
	Female	18 19	22 23
Cartilage of first rib	Male and female	26 27	

E DENTAL AGE (see Tables 1 and 2)

- 1 Determined by
 - a Number of teeth
 - b Roentgen films for development of 6 12 and 18 year-old molars
- 2 Comments
 - a Retention of deciduous teeth may not indicate actual dental age
 - b Progress of secondary teeth as shown by roentgenograms is a better index

F SEXUAL DEVELOPMENT

- 1 Boys (see Table 4)
 - a Breasts may enlarge at pubescence for a short period
 - b Penis
 - (1) Erections may occur
 - (a) At any age
 - (b) In definite eunuchoids
 - (2) Measurement is of little importance before 11 or 12 years
 - (3) It is buried under fat in many
 - (4) Increase in size precedes growth of pubic hair
 - c Testes
 - (1) Size
 - (a) Measure
 - [1] Length
 - [2] Width
 - [3] Thickness
 - (b) Little or no change before advent of pubescence
 - (2) Volume may be estimated by use of models (see Fig 15)
 - (3) Biopsy (see Figs 3 7)
- 2 Girls (Figs 3 4 5 6 7)
 - a Pubic hair precedes menarche
 - b Slight breast development appears before pubic hair growth
- 3 In both sexes pubic hair grows before the axillary hair, but the reverse is possible¹⁸

G EVALUATION OF VARIABLES

- 1 By summarizing the different ages and behavior patterns⁹ in normal school children including psychometric determinations an over all estimate (organismic age¹⁷) of a 10 year old child's capacity for physical and mental development is said to have prognostic significance as judged by his performances and evaluation again at 18 years of age

- 2 Perhaps too much emphasis should not be placed on these surveys in individual cases as regards prediction of mental achievement
- 3 Exceptionally bright children may approach the mean at maturity, while somewhat retarded children may advance⁵
- 4 A similar assessment is also undoubtedly applicable to endocrine cases

VI VARIATIONS OF NORMAL PUBESCENCE

A ABNORMALITIES USUALLY ATTRACTING ATTENTION

- 1 Obesity
- 2 Small genitalia

B ADIPOSEGENITAL DYSPLASIA—Froehlich's syndrome (see 3)

- 1 Obesity and small genitalia are frequently so labeled
- 2 The term was originally coined by Bartels¹ to describe a case of retarded growth and sexual development with obesity which was not different in any way from Froehlich's syndrome
- 3 The term should be restricted to this usage
- 4 Fat boys at pubescence with undeveloped genitalia are not deficient in pituitary follicle stimulating hormone (FSH)¹ ¹⁸ but rather may be temporarily deficient in luteinizing hormone (LH) (see Figs 8 11)
- 5 Until sufficient stimulation of the gonads takes place no increase in size of testes or penis may occur
- 6 If height age or growth rate is normal and if testes show form even though of prepubescent size puberty will follow in all probability
- 7 For causes of obesity see 97 II

C EXTERNAL HYPOGENITALISM¹

- 1 This term should be employed to denote a disproportionate smallness of penis and testis in relation to general somatic development which is usually indicated by height age
- 2 Prepubescent size of genitalia may remain constant until beginning of pubescence

- 3 In most instances, hypogonitalism is apparent and not real due to excessive fat (see Figs 13 and 14)
- 4 Hypogonitalism of pituitary dwarfs is not disproportionate to somatic development and therefore is not true hypogonitalism (see 3 XIV)
- 5 True external hypogonitalism may be present
 - From birth
 - b In prepuberal eunuchoidism, but is not often ascertained until after 13 to 15 years
- 6 Transient external hypogonitalism
 - a In some boys, growth and skeletal maturation may exceed genital development at or beyond the usual age of pubescence
 - b Until genital development begins, a transient hypogonitalism may exist

D DIFFERENTIAL DIAGNOSIS

1 Resume of normal data

- a Mental
 - (1) Age
 - (2) Responsiveness
- b Growth rate, as shown by school records
- c Height
 - (1) Above average is common
 - (2) Trend in familial heights should be studied
- d Signs of early breast development in both sexes
 - Penis may be hidden in excess fat so that actual proportions are not evident
- f Testes
 - (1) Consistency—firm
 - (2) Size for age—up to 11 years very slight growth may take place therefore of little value in diagnosis
 - Serum phosphorus (inorganic fast ing)—above 4.5 mg % until 12 or 14 years
- h Urinary FSH—greater than 6 mU/24 hrs
 - i Sella turcica
 - j Bone age—within 12 months of chronologic age by Todd's standards (see Fig 19)

2 Delayed pubescence (see Fig 12)

- a Introduction—this can be rightly termed an endocrine disorder in point of time, just as sexual precocity is considered abnormal
- b Mental age—variable
- c Obesity—common
- d Growth
 - (1) Rate continues normally
 - (2) Height may often be above average
 - (3) Span is increased, producing eunuchoid appearance with recovery at ages of 16 to 20 years (transient eunuchoidism)
 - (4) Theoretically, these findings may be due to delayed secretion of luteinizing hormone (LH)
- e Breasts—may be slightly enlarged in both sexes
- f Secondary sexual characteristics—delayed in male and female
- g Testes
 - (1) Consistency—firm
 - (2) Size
 - (a) Normal prepubescent
 - (b) Increases (also penis) over 6 to 12 month period of observation
 - (3) Biopsy—normal but retarded development
- h Menses—absent
 - i Serum phosphorus (inorganic fast ing)—above 4.5 mg %
 - j Urinary hormone assays
 - (1) FSH
 - (a) Normal
 - (b) Increased rarely
 - (2) 17 ketosteroids—low for age
- k Sella turcica—normal
- l Bone age
 - (1) Normal
 - (2) Decreased
- m Chorionic gonadotropin given to males increases
 - (1) 17 ketosteroid excretion
 - (2) Nitrogen retention

3 Selective gonadotropic deficiency may lead to eunuchoidism

- a Early
 - (1) Weight—may be increased
 - (2) Height—slightly increased

- (3) Span—normal
- (4) Breast development—absent in females
- (5) Testes and penis—may be small for age
- (6) Serum phosphorus (inorganic fasting) — normal above 4.5 mg %
- (7) Urinary FSH — absent less than 10 mu/24 hrs
- (8) Bone age—retarded a little

b Late

- (1) Weight—may be increased
- (2) Height—often above normal
- (3) Span—greater than height
- (4) Pubic or axillary hair
 - (a) Absent
 - (b) Scant
- (5) Secondary sexual characteristics—absent
- (6) Urinary hormone assays
 - (a) FSH—absent
 - (b) 17 ketosteroids—low
- (7) Bone age—retarded

c Comment—differentiation of this condition from delayed pubescence before the age of 15 is most difficult

4 Primary disease of gonads leading to eunuchoidism

a Early

- (1) Weight—may be increased
- (2) Height—slightly increased but may be subnormal
- (3) Span—normal
- (4) Breast development—absent
- (5) Testes
 - (a) Consistency—soft or mushy
 - (b) Size—minuscule or absent
 - (c) Biopsy—evidence of destructive disease

(6) Bone age—retarded somewhat

b Late

- (1) Weight—may be increased
- (2) Height—well above average
- (3) Span—greater than height
- (4) Axillary and pubic hair—scant and some facial hair—possibly present
- (5) Breast development—delayed
- (6) External genitalia—retarded
- (7) Testicular biopsy—as above

(8) Urinary hormone assays

- (a) FSH—positive
- (b) 17 ketosteroids—variable

(9) Bone age—retarded

E TREATMENT

1 General

- a Obesity, when present should be first point of attack
- b Glandular therapy should be postponed until 14 or 15 years of age pending observations which indicate beginning and progressing pubescence unless primary testicular disease is proved
- c True hypogonadism as defined above is an indication for therapy

2 External hypogonadism in

a Infancy

- (1) Indications—see above
- (2) Methyltestosterone injection—1 to 2 mg daily
- (3) Result—development may occur

b Pubescence

- (1) Indications—see delayed pubescence
- (2) Methyltestosterone oral—5 to 20 mg daily
- (3) Result—growth of genitalia may be observed

3 Hormonal

a Chorionic gonadotropin for males

(1) Indications

- (a) True external hypogonadism—as a trial

(b) Delayed pubescence

- [1] If no progress in size of genitalia by age 14 under observation or earlier for psychologic reasons
- [2] After exclusion of primary testicular disease
- [3] To differentiate after age of 14 between hypogonadotropic (primary testicular disease) and hypogonadotropic (secondary testicular failure) deficiency

- (2) Dosage: intramuscular—1,000 to 3,000 units per week for 2 to 4 months
- (3) Result—initiation of pubescence if testes are responsive
- b Testosterone for males
 - (1) Indications
 - (a) Same as for chorionic gonadotropin
 - (b) Primary testicular disease especially (see 47 XVI A, B 1)
 - (2) Dosage
 - (a) Methyltestosterone, oral—10 to 20 mg daily for 2 to 6 months
 - (b) Testosterone propionate, intramuscular—10 to 20 mg per week for 2 to 6 months
 - (3) Results
 - (a) True pubescence initiated in some
 - (b) Substitutional development of penis and secondary sex characteristics
- c Estrogens for females
 - (1) Indication — delayed pubescence of any type after 14 years of age
 - (2) Dosage stilbestrol or other estrogen preparations, oral—0.1 to 0.3 mg daily for 2 to 4 months or longer
 - (3) Results
 - (a) True menarche may follow
 - (b) Substitutional development of secondary sex characteristics, including uterus and external genitalia

F PROGNOSIS

- 1 Generally favorable even without therapy
- 2 Nonresponsive cases require further studies to determine outcome

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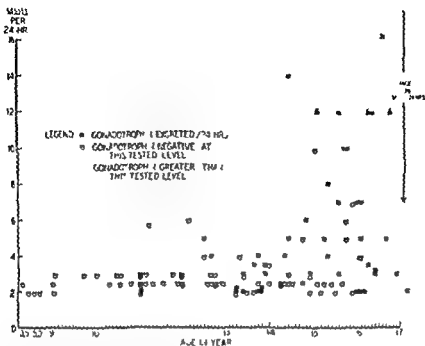


CHART 1 NORMAL DEVELOPMENT Urinary excretion of gonadotropin (FSH) in normal boys according to chronologic age (9 to 17 years of age) Note wide variations and the rather large number of cases that have very little output between 13 and 16 years It is obvious that no prognostic significance can be attached to such determinations MUU = mouse uterine units (Greulich W W Dorfman R I Catchpole H R Solomon C I and Culotta C S Somatic and Endocrine Studies of Puberal and Adolescent Boys Washington D C Child Development Publications of the Society for Research in Child Development National Research Council p 54)

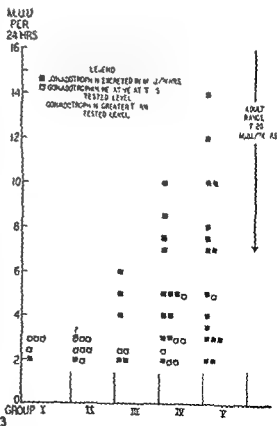


CHART 2 URINARY EXCRETION OF GONADOTROPIN ACCORDING TO DEVELOPMENTAL GROUP STATUS IN NORMAL BOYS A better correlation exists here showing that the physical status is as good an index of development as the measurements of gonadotropin (FSH) MUU = mouse uterine units (Greulich W W Dorfman R I Catchpole H R Solomon C I and Culotta C S Somatic and Endocrine Studies of Puberal and Adolescent Boys Washington D C Child Development Publications of the Society for Research in Child Development National Research Council p 55)

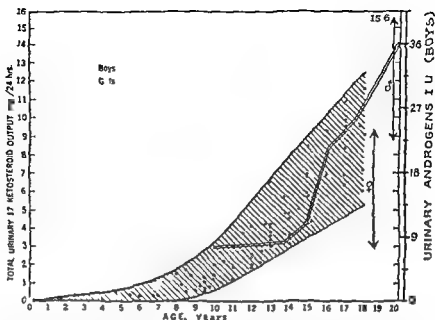


CHART 3 17 KETOSTEROIDS Total urinary 17 ketosteroids (including estrogens) in boys and girls along with biologically assayed androgens (double line) in boys up to 20 years of age. The average range of 17 ketosteroids for males and females is shown in vertical lines at the right. Note that males have greater quantities. The wide variation in individual cases during pubescence and puberty demonstrates the limited value of these determinations. The degree and the progression of genital development provide a more reliable index than estimation of these studies (Greulich W W, Dorfman R I, Catchpole H C, Solomon C I and Culotta C S. Somatic and Endocrine Studies of Puberal and Adolescent Boys. Washington D C: Child Development Publications of the Society for Research in Child Development, National Research Council pp 25-35. Levine S Z, Butler A M, Holt L E Jr and Welch T A. Advances in Pediatrics Vol II. New York and London: Interscience Publishers Inc p 272).

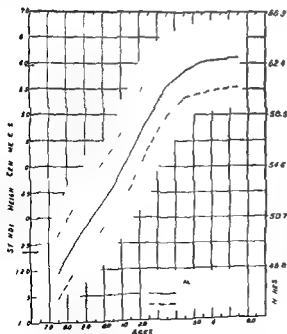


CHART 4 GROWTH AND MENARCHE Growth trends in average height of girls with same age of onset of menarche (13 to 13.5 years). The groups are divided into the tallest, the middle and the shortest cases. This chart shows that based on averages the final height in 2 girls with menarche at the same age probably can be predicted according to their height at menarche (Shuttleworth F K. Sexual Maturation and the Physical Growth of Girls Age 6 to 19. Child Development Publications of the Society for Research in Child Development, National Research Council, Washington D C p 39).

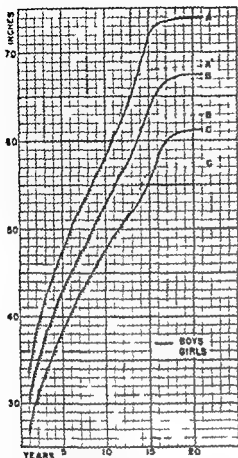


CHART 5 HEIGHT CHART This graph shows the average curves (B and B¹) for boys and girls and the extremes (A and A¹) which are the 99 percentile curves meaning that 99% of children are below these measurements while C and C¹ are the one percentile curves. Height age may be calculated from the curves by finding measured height of subject on curve B for boys and B¹ for girls and reading off the figure at the bottom of the chart (Burgess VI A The construction of two height charts J of Am Statistical Assn 32 290)

CHART 6 NORMAL DEVELOPMENT Height and growth trends in earliest menarcheal Group A (before 11½ years) and in latest menarcheal Group B (14 to 15 years). The cross hatching of each curve represents the standard deviation in each group. Note that younger maturing girls on the average reach an earlier plateau (Shuttleworth F K Sexual Maturation and the Physical Growth of Girls Age 6 to 19 Child Development Publications of the Society for Research in Child Development National Research Council Washington D C p 53)

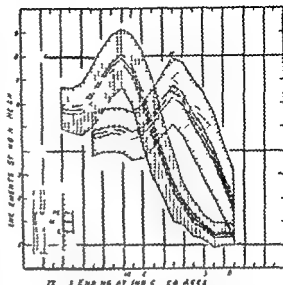
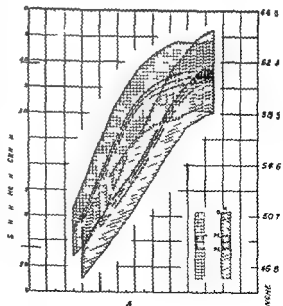


CHART 7 GROWTH AND MENARCHE Average annual increments in height of girls having early (A) and late (B) menarche. It will be noted that the pubertal spurt in growth is delayed in cases with late menarche. Thus prediction of final height can be estimated only from time of menarche or shortly thereafter. The fall in annual increment probably corresponds with decrease in growth hormone secretion (Shuttleworth F K Sexual Maturation and the Physical Growth of Girls Age 6 to 19 Child Development Publications of the Society for Research in Child Development National Research Council Washington D C p 56)



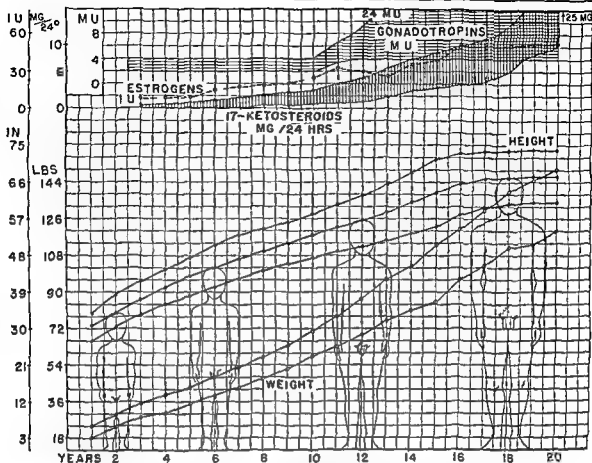


CHART 8 NORMAL DEVELOPMENT IN THE MALE Body proportions and secondary sex characteristics are plotted with weight and height curves Average height 50 percentile curve is between 99 (top) and 1 (bottom) percentile lines (Burgess) Urinary hormone assays are indicated on top of the graph Gonadotropin and 17 ketosteroid levels exceed chart space

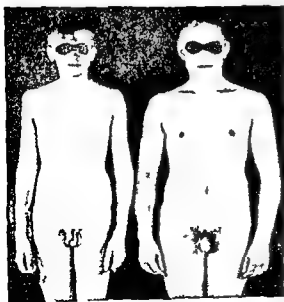


FIG 1 VARIATION IN NORMAL DEVELOPMENT Boys of same chronologic age (14.2 years) but with a somatic age of 12.4 years on the left and 16.8 years on the right Both boys normal Note difference in height

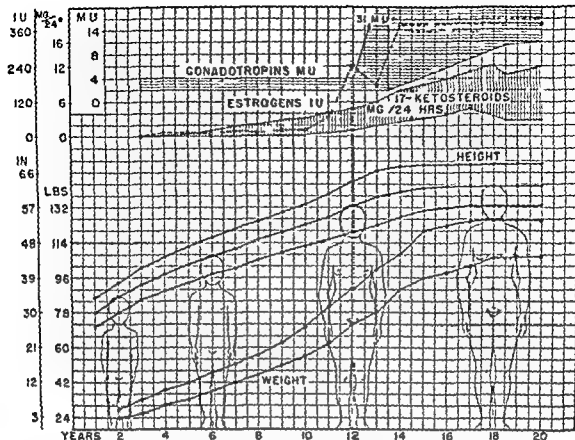


CHART 9 NORMAL DEVELOPMENT IN THE FEMALE Body proportions and secondary sexual development are plotted with weight and height curves Average height 50 percentile curve is between the 99 (top) and 1 (bottom) percentile lines (Burgess) Urinary hormone findings are included Gonadotropin levels exceed chart space After menarche the estrogen levels vary with the menstrual cycle

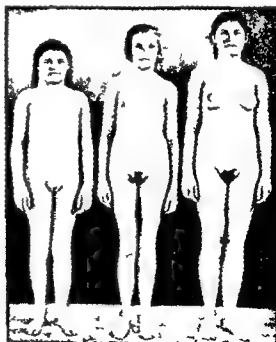


FIG 2 VARIATIONS IN HEIGHT AND SECONDARY SEX DEVELOPMENT Normal girls from 13 to 14 years of age (Priesel R and Wagner R Gesetzmassigkeiten im Auftreten der extragenitalen sekundaren Geschlechtsmerkmale bei Madchen Zeitschrift fur Konstitutionslehre 15 333)

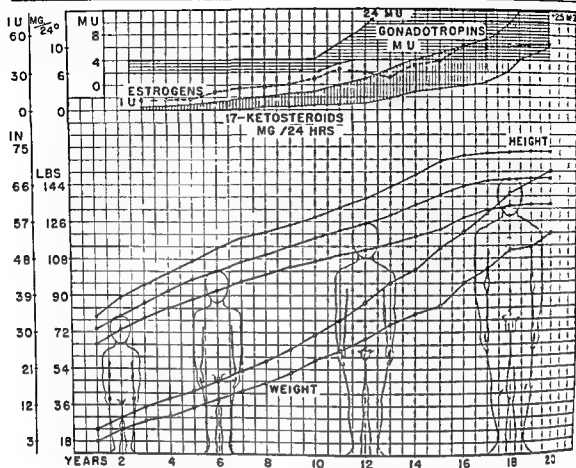


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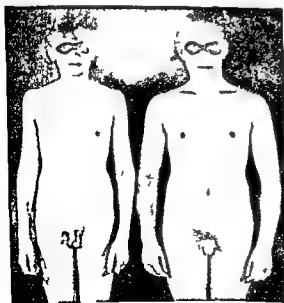


FIG 1 VARIATION IN NORMAL DEVELOPMENT Boys of same chronologic age (14.2 years) but with a somatic age of 12.4 years on the left and 16.8 years on the right. Both boys normal. Note difference in height.

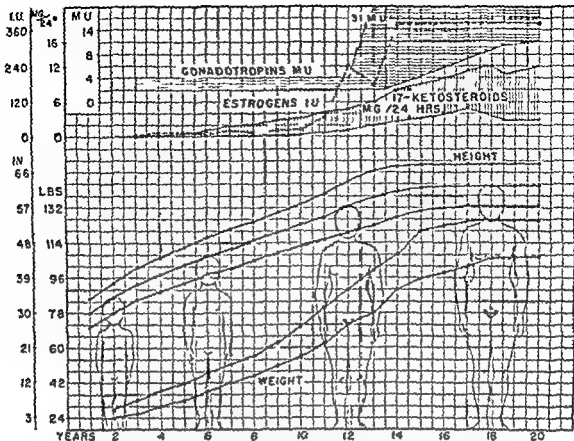


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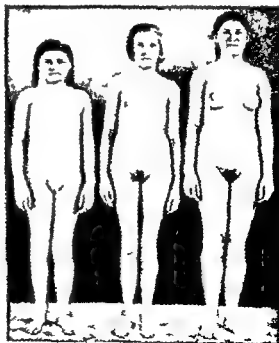


FIG 2 VARIATIONS IN HEIGHT AND SECONDARY SEX DEVELOPMENT Normal girls from 13 to 14 years of age (Priesel R and Wagner R Gesetzmassigkeiten im Auftreten der extragenitalen sekundaren Geschlechtsmerkmale bei Madchen Zeitschrift fur Konstitutionslehre 15 333)



FIG 3 SEVEN YEAR OLD TESTIS—NORMAL Tubules close together No Leydig cells Tubular cells not clearly differentiated probably mostly Sertoli cells few cells suggest early spermatogonia Postmortem specimen [(left) x 90, (right) x 370]

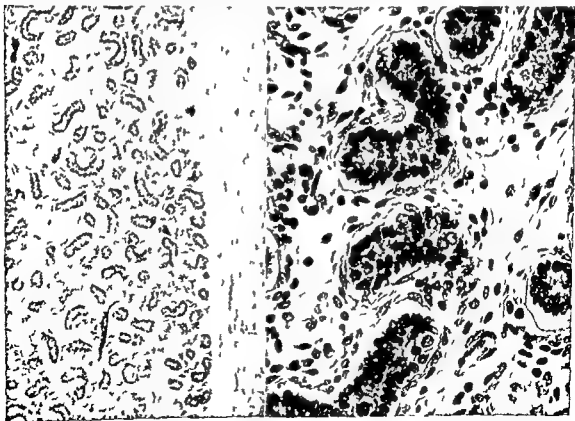


FIG 4 SEVEN YEAR OLD TESTIS—CRANIOPHARYNGIOMA Tubules widely spaced Spermatogonia clearly present Specimen illustrates variation at this age In this case spermatogonia would suggest greater maturity than in a 7 year old normal Postmortem specimen [(left) x 78 (right) x 380]

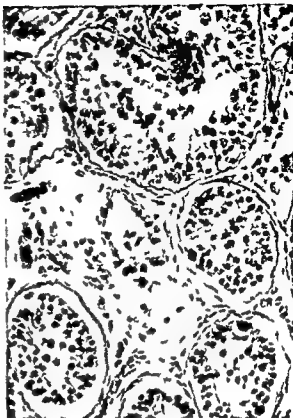


FIG 5 (Top, left) THIRTEEN YEAR-OLD TESTIS—NORMAL Tubules close together Greater maturation than at 7 years Evidence of Leydig cell formation scanty Post mortem specimen (x 27)

FIG 6 (Top right) NINETEEN YEAR OLD TESTIS—NORMAL Very little interstitial connective tissue Spermatocytes and spermatozoa present Leydig cells evident but not prominent Post mortem specimen (x 175)

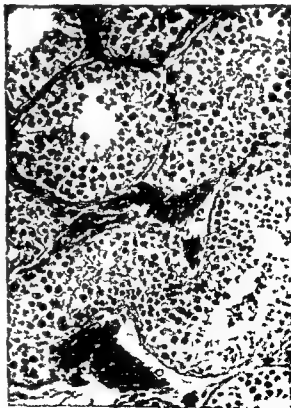


FIG 7 (Bottom) ADULT TESTIS (See also Fig 288) Age 57 All phases of spermatogenesis present Cluster of Leydig cells in center Some thickening of basement membrane which is not infrequent at this age Castration specimen (x 265) (Drs Vernon P Dick and William A Meissner)

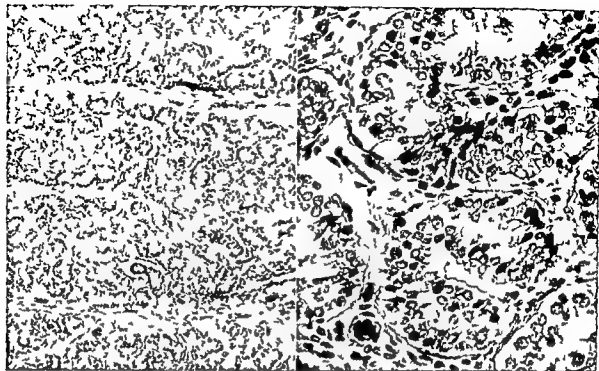


FIG 3 SEVEN YEAR OLD TESTIS—NORMAL Tubules close together No Leydig cells Tubular cells not clearly differentiated probably mostly Sertoli cells, few cells suggest early spermatogonia Postmortem specimen [(left) $\times 90$, (right) $\times 370$]

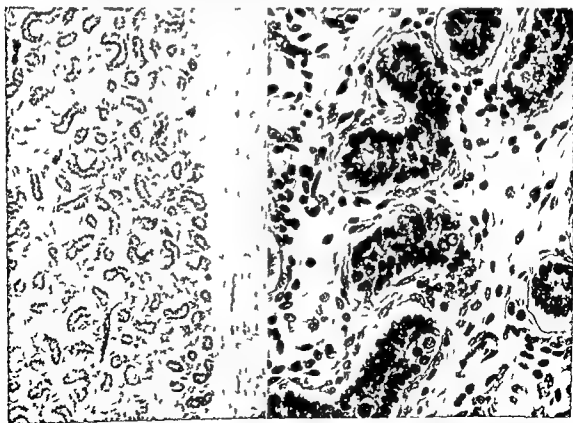


FIG 4 SEVEN YEAR OLD TESTIS—CRANIOPHARYNGIOMA Tubules widely spaced Spermatogonia clearly present Specimen illustrates variation at this age In this case spermatogonia would suggest greater maturity than in a 7 year old normal Postmortem specimen [(left) $\times 78$ (right) $\times 380$]

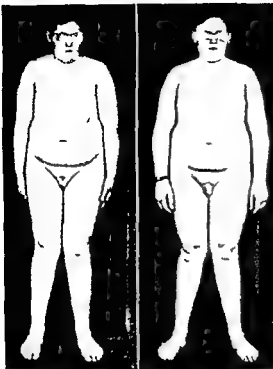


FIG 10 HYPOGENITALISM RESPONDING TO TESTOSTERONE (Left) Fourteen year old boy after 1 year of unsuccessful therapy elsewhere with chorionic hormone—1 000 units weekly (question of sufficient quantity) Weight 170 lbs Height 60½ in Height age 14 years Bone age 14 years Urinary follicle stimulating hormone (FSH) test was negative on 2 occasions (less than 80 m u) 17 ketosteroids 3.4 mg in 24 hrs The volume of each testis was less than 2 cc For 3 months unsuccessful attempts were made to diet for weight reduction Meanwhile there was growth of ¾ in (Right) After 25 days of methyltestosterone 30 mg per day volume of the testis increased to 5 cc Dose reduced to 10 mg daily for 3 months then discontinued Right testis re-entered canal thereafter (Hurxthal L M Hypogenitalism during the usual time of puberty J A M A 136 12)

FIG 11 CONDITION OF BOY SHOWN IN FIGURE 10 TWO YEARS LATER WITH NO TREATMENT Height 64 in Height age 15½ years Pubic hair growing Penis length normal Volume of left testis about 18 ml Right testis in canal Erections Progress satisfactory except for weight Pinkish striae developed after renewed and partially successful attempts at weight reduction Both testes in scrotum at 18 with normal secondary sexual characteristics

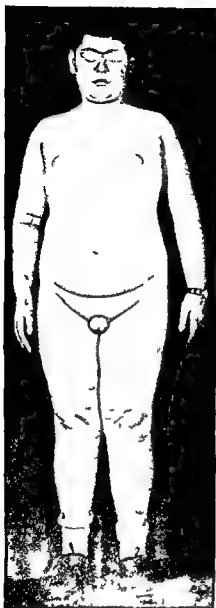


FIG 8 MODERATE OBESITY AND APPARENT EXTERNAL HYPAGONADISM IN A PUBESCENT BOY Age 12 years Height 61 in Height age 14 years Penis hidden in pubic fat Volume of each testis approximately 4 cc The size of the testes indicates pubescence is under way The height precludes hypogonadism This case cannot be classified as hypogonadism because the genitalia are normal in relation to somatic development The prominent breasts are an indication of pubescence

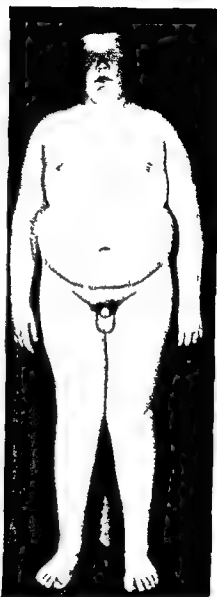


FIG 9 OBESITY IN PUBESCENT BOY Note hippy distribution of fat and prominence of breasts It is often impossible to determine whether breast size is due to obesity alone or to pubescence The genital development is normal for age in every way No endocrine disorder This is the usual outcome of fat boys with seemingly small genitals over which some parents are greatly concerned

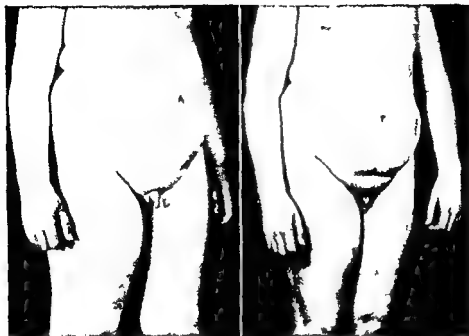


FIG 14 PREPUBESCENT BOY WITH APPARENT HYPAGONADISM (*Left*) The penis looks small because of massive obesity (160 lbs) The testes were in the lower inguinal canal but had been seen in scrotum by parent estimated to be 2 cc in volume Age 11 years Height 61½ in Height age 14 years Bone age 14 years Administration of 10 000 units of chorionic hormone was followed by slight further descent of testes and progression in size thereafter Follicle stimulating hormone (FSH) test was positive estimated at more than 30 and less than 80 m u per liter before therapy Urinary estrogens—2 plus (*Right*) Four years later Weight 209 lbs Height 68½ in Height age 18 years Testis 10 cc volume Penis normal although largely buried in mons Periodic attempts at dieting unsuccessful The effect of chorionic gonadotropin was indefinite in this case although it may have initiated testicular growth (Hurxthal L M Hypogonadism during the usual time of puberty J A M A 136 12)



FIG 15 MODELS USED FOR ESTIMATION OF TESTICULAR SIZE The smallest represents 2 cc volume which is normal until pubescence The largest volume 18 cc is usually found in a normal 18 year old boy or over The intermediate models represent growth from the beginning of pubescence until its termination (Hurxthal L M Hypogonadism during the usual time of puberty J A M A 136 12)



FIG 12 DELAYED PUBERTY WITH NORMAL OUTCOME *Family history* Father 69 in Mother 62 in One brother age 15 years height 57 in Another brother age 16 height 58 in *History of present illness* Normal libido Frequent erections Bed wetter until 16 years Good health *Physical examination* Age 17 years Weight 110 lbs Height 57 in Height age 12 years Bone age 14½ years No axillary hair Few pubic hairs Volume of testis 5 in 6 cc *Laboratory findings* Urine and blood normal Plasma cholesterol 175 mg % Urinary hormone assays FSH negative (unconcentrated) and 17 ketosteroids 1 mg/24 hrs *Comment* No treatment recommended He served 3 years in the Army having been inducted at age of 18 years Final height at 21 years was 64 in No explanation was found for this delay in puberty



FIG 13 APPARENT HYPOGENITALISM (Top) Appearance when standing with legs together (Bottom) Close up view taken at same time legs apart Testis volume 2 cc normal for his age of 6

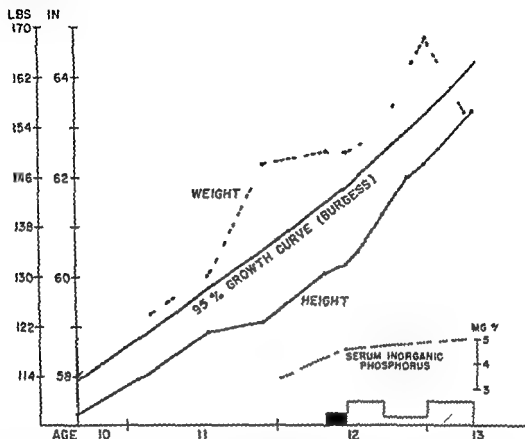


CHART 10 CRYPTORCHIDISM APPARENT HYPOGENITALISM AND OBESITY (See also Figs 16 and 17) Patient was treated by his family physician from the age of 6 to 9 years with chorionic gonadotropin and small doses of testosterone. Treatment was discontinued 1 year before first observation. In view of the normal bone age and urinary 17 ketosteroids no therapy was advised. Fifteen months after his first observation there was a slowing down in growth and no further genital development. Testicular biopsy taken at the age of 12 was about the average for an 8 year old (see Fig 17). Fasting serum inorganic phosphorus (3.4 mg %) was low. Note gain in weight during retardation of growth. No increase in size of penis or testes for 9 more months. Then chorionic gonadotropin—4 000 units weekly—was given for 6 weeks with noticeable effect on size of testes and number of erections. With methyltestosterone 2½ to 5 mg daily there probably was an increased growth rate. Serum inorganic phosphorus levels increased concomitantly. When methyltestosterone dosage was decreased growth rate continued. Weight loss was due to more careful dieting. This case illustrates a transient decline in growth rate cause unknown, the histology of the testes in a prepubescent boy—in whom the bone age and 17 ketosteroid output was normal in spite of absence of Leydig cells. Therapy was instituted first because of growth lag and secondly to hasten development of genitalia for psychologic reasons. No therapeutic success can be claimed for this boy except possibly as regards genital enlargement. No apparent harm results from this type of priming therapy and often pubescence is initiated. Solid area chorionic gonadotropin—4 000 units per week. Hatched area methyltestosterone—2 and 5 mg sublingually daily.

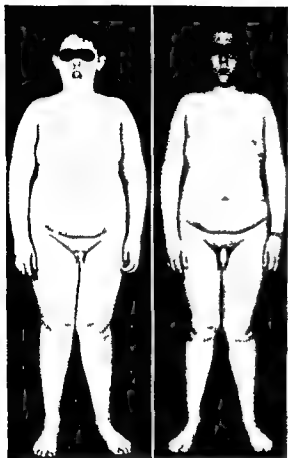


FIG 16 CRYPTORCHIDISM OBESITY AND HYPOGENITALISM IN A BOY ABOVE AVERAGE HEIGHT (See also Fig 1; and Chart 10) *Chief complaint* Obesity. *History of present illness* Overweight since the age of 3. Retarded genital development. Undescended testes noted at the age of 5. From the age of 6 chorionic gonadotropin had been administered almost continuously until the age of 8. Testosterone propionate 5 mg. was then given weekly for 1 year. (Patient has been treated elsewhere.) Testes descended. Perfectly well. *Physical examination* Age 10 Height 57½ in. Height age 12½ years. Testis volume 2 cc. Photograph (left) taken at age 12. *Laboratory data* Urinary hormone assays: FSH (unconcentrated) negative and 17 ketosteroids 9.3 mg/24 hrs. *Röntgenographic findings* Bone age 12½ years. (Right) Age 13 years. Weight 156 lbs. Height 63½ in. Some pubic hair. Penis 3.6 in. Testis volume 10 cc. After cessation of therapy progress continued.



FIG 17 TESTICULAR BIOPSY (See also FIG III and CHART 10) Specimen taken at age 12 before therapy. (Left) Low power magnification. (right) high power magnification. Seminiferous tubules—width—very small just beyond cord stage. Sertoli cells—present. Cells of spermatogenesis—spermatogonia very rare. lumen—small filled with debris. basement membrane—normal. indistinct. Leydig cells—none. Interstitial tissue—increased but probably normal for stage of development. Blood vessels—normal.

FIG 19 OUTLINES OF RADIOGRAPHS OF SKELETAL DEVELOPMENT AT DIFFERENT AGES
(Drawn from Todd T W Atlas of Skeletal Maturation St Louis Mo by)

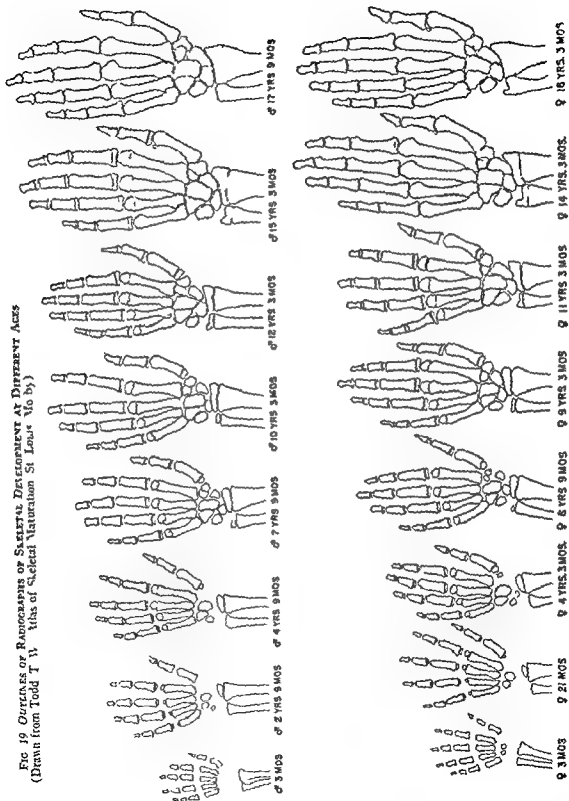




FIG 18 OSSIFICATION INDEX Diagrammatic representation of the development and latest ages (in circles) of the ossification centers in the normal. Extremes of normal ranges are listed below. The ossification index devised by Leonard may be computed when one or more centers have not appeared at the usual time in which case ossification is retarded

BONE	EARLIEST	LATEST Months	MAJORITY Months
Capitate	Birth	6	2½
Hamate	Birth	7	3½
	Years	Years	Years
Radius (epiphysis)	½	2	1
Triquetrum	1	4	2¼
Lunate	2	5	4
Navicular	4	6	5
Lesser multangular	4	7	5¼
Greater multangular	4	7	5¼
Ulna (epiphysis)	5	8	6¾

(Leonard D W Early recognition of endocrine disorders in childhood by roentgenograms of the wrist to determine the Ossification Index Am J Roentgenol 53 55)

CHAPTER 2

Pituitary

PRECLINICAL

Section 2 PRELIMINARY

- I HISTORY
- II ANATOMY
- III EMBRYOLOGY
- IV CONGENITAL ANOMALIES
- V HISTOLOGY
- VI FUNCTIONS
- VII CHEMISTRY
- VIII BIO ASSAY
- IX PATHOLOGY
- X CLASSIFICATIONS
- XI CHIEF CLINICAL FINDINGS OF HYPOSECRETION
- XII CHIEF CLINICAL FINDINGS OF HYPERSECRETION
- XIII EXAMINATION OF PATIENT
- XIV SELLA TURCICA

CLINICAL

Section

- 3 PREPUBERAL HYPOPITUITARISM
 - 4 POSTPUBERAL HYPOPITUITARISM
 - 5 SIMMONDS DISEASE
 - 6 PITUITARY MYXEDEMA
 - 7 PITUITARY ADRENAL INSUFFICIENCY
 - 8 DIABETES INSIPIDUS
 - 9 GIGANTISM
 - 10 ACROMEGALY
 - 11 CUSHINGS SYNDROME (BASOPHILISM)
 - 12 CHROMOPHOBE TUMORS
 - 13 SUMMARY OF TUMORS
-

SECTION 2

PRELIMINARY

I HISTORY

AD 130-200	Galen ^m	Pituitary discovered
1543	Vesalius ⁶²	This gland has an excretory function
1703	Willis ⁶⁴	Control of cerebrospinal fluid by it
1724	Santorini ¹⁷	Anterior lobe described
1759	Haen ⁶⁵	Amenorrhea occurred with pituitary tumor
1778	Sommerring ⁶⁶	Pituitary named 'hypophysis
1794	Frank ²³	Diabetes mellitus and diabetes insipidus differentiated
1801	Saucerotte ¹³	First clinical account of a case later known to be acromegaly
1838	Rathke ⁶¹	Comparative anatomy and embryology of the gland described
1840	Mohr ³³	Obesity with invasive pituitary tumor reported
1864	Verga ⁶¹	First autopsied acromegalic case recorded
1884	Fritsche and Klebs ⁷¹	Enlarged pituitary in a giant
1885	Wadsworth ²²	Myxedema may be caused by a pituitary tumor
1886	Horsley ⁷²	Hypophysectomy successfully performed in dogs
1886	Marie ²⁴	Term 'acromegaly' originated
1871	Faneau de la Cour ¹	'Infantilism' is due to hypopituitarism
1887	Winkowski ⁷⁷	Pituitary enlargement found in acromegaly
1888	Rogowitsch ⁴¹	Thyroidectomy produced an increase in size of hypophysis
1891	Paultauf ⁶¹	Pituitary dwarfism described
1892	Vassale and Sacchi ⁶⁰	Anterior lobe injury promoted polyuria
1893	Caton and Paul ³	Acromegaly treated by cerebral surgery (unsuccessful)
1894	Tamburinni ⁵⁷	Hyperactivity and hypertrophy of the pituitary causes acromegaly
1895	Oliver and Schafer ³⁹	Pressor action of posterior pituitary extracts discussed
1898	Comte ¹³	Pregnancy produces hypophyseal enlargement
1900	Babinski ⁴	Adiposogenitalis noted
1900	Benda ⁶	Fosinophilic cells of pituitary are increased in acromegaly
1901	Frohlich ²⁵	Syndrome of dwarfism, delayed sexual development and pituitary tumor described
1906	Cushing ¹⁸	Sexual infantilism with optic atrophy observed in pituitary tumors
1906	Schlosser ⁶⁰	Successful cerebral operation performed on acromegalic patient
1908	Bartels ⁶	Term adiposogenitalis coined
1908	Paulesco ⁴⁹	Removal of anterior lobe was fatal whereas posterior lobe produced negative results
1909	Aschner ³	Anterior lobe removal accomplished successfully in dogs
1909	Bell ⁷	Posterior pituitary extracts used in obstetrics
1909	Dale ¹⁷	Oxytocic action shown in posterior pituitary extracts
1910	Crowe Cushing and Homans ¹⁴	Complete hypophysectomy in dogs led to death of the animals with peculiar and characteristic symptoms (cachexia hypophysopriva)
1911	Hirsch ²⁹	Endonasal method introduced for surgery of pituitary tumors
1913	Goldzieher ²⁷	Diabetes insipidus is due to a destructive lesion in pituitary
1914	Simmonds	Fatal cachexia caused by pituitary failure
1916	Erdheim ⁸	Pituitary dwarfism ('nanosomia pituitaria') recognized
1917	Allen ¹	Thyroid atrophy resulted from absence of pituitary
1918	Hofbauer ⁴⁰	Eclampsia may be due to hypersecretion of posterior lobe
1921	Evans and Long ¹⁹	Growth promoting influence of anterior pituitary demonstrated

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- b Infundibulum (neural stalk)
- (1) Pediculus infundibularis (stem)
 - (2) Bulbus infundibularis (bulb)
 - (3) Labrum infundibularis (rim) or median eminence of tuber cinereum
- Hypophyseal stalk is made of
- (1) Neural stalk
 - (2) Sheath of portions of lobus glandularis

C WEIGHT—^{3 6 10}

	Gm
1 Range	0.4 to 1.8
2 Average (males and females)	0.57
a Males	
(1) Distalis	0.3941
(2) Intermedia	0.0108 (with colloid)
(3) Nervosa	0.1206
(4) Total	0.5255
b Females	
(1) Distalis	0.4990
(2) Intermedia	0.0094 (with colloid)
(3) Nervosa	0.1101
(4) Total	0.6185
3 Variation in normal	(see 2 V D) ^{1 2}
a Birth	100 mg
b Early childhood	
(1) First year	150 mg
(2) Third year	300 mg
(3) Seventh year	One half of the adult size
(4) Near or at puberty	Five sixths of its maximum size
■ Adolescence	Maximum possibly not until 25
d Both sexes	
(1) With aging, increase in	
(a) Pars intermedia	
(b) Neural lobe	
(2) Tall people have larger pituitaries	
■ Males—after middle age pars distalis decreases	
f Females	
(1) Larger pituitaries than males	
(2) Pregnancy increases weight of gland	

D SIZE⁶

- 1 Variable dimensions reported
- 2 Average 10 x 13 x 6 mm

E BLOOD AND LYMPH SUPPLY⁷

- 1 Arteries
 - a Superior hypophyseal arteries from
 - (1) Internal carotids
 - (2) Circle of Willis
 - b Inferior hypophyseal arteries from internal carotids
- 2 Veins
 - a Portal venules arise from deep and superficial plexuses of stalk
 - b Termination in cavernous sinuses
 - c Systemic venules do not exist
- 3 Lymphatics—very little known

F NERVES^{4 8}

- 1 Processus infundibuli receives majority of fibers from hypothalamus (hypothalamico hypophyseal tract) which arise in
 - a Supra optic nuclei
 - b Tuber cinereum
- 2 This tract may possibly send a few fibers to pars
 - a Intermedia
 - b Tuberalis
 - c Distalis
- 3 Carotid plexus sends unmyelinated fibers (sympathetic fibers mostly) to pars distalis
- 4 Parasympathetic fibers from glossopharyngeal nerve may be found
- 5 Secretory activity of pituitary may be stimulated through the cervical sympathetic tracts
- 6 The exact innervation is not known definitely

III EMBRYOLOGY¹

A FORMATION OF HYPOPHYSEAL PARTS

- 1 An evagination (Rathke's pouch) from the primitive buccal cavity (stomodaenum) forms the anterior lobe
- 2 This pouch grows dorsally to meet a hollow diverticulum extending down from the floor of the third ventricle which becomes the
 - a Pars nervosa of the posterior lobe
 - b Pituitary stalk (infundibulum)
- 3 The pars nervosa pushes into and obliterates the pouch's cavity, leaving a narrow cleft

1922	Philip Smith ³	Pituitary extracts or implants prevented atrophy of other endocrine glands in hypophysectomized animals
1924	Rasmussen ⁴³	Pituitary cytology analyzed
1924	Starling and Varney ⁵	Pituitrin action on renal flow noted
1927	Zondek and Aschheim ^{60 67}	Gonadotropic hormone of anterior pituitary demonstrated
1928	Aschheim and Zondek ⁶	Pregnancy urine has gonadotropic activity ("A Z" test)
1928	Kamm et al ³³	Posterior lobe extract separated into two principles—oxytocin and vasopressin
1928	Stricker and Grueter ⁶	Lactation controlled through pituitary
1928	Uhlenhuth and Schwartzbach ⁹	Thyrotropic hormone discovered
1929	Engle ¹⁸	Castration increases pituitary gonadotropic activity
1929	Teel and Watkins ⁴⁸	Elevation of blood inorganic phosphorus was found after administration of pituitary extracts
1930	Cole and Hart ¹⁰	Gonadotropin isolated from pregnant mare serum
1930	Houssay and Biasotti ³	Diabetes caused by pancreatectomy in dogs could be improved by hypophysectomy
1930	Philipp ⁴²	Pregnancy urine gonadotropins are of placental origin
1930	Schapiro ⁴⁰	Cryptorchidism treated effectively with chorionic gonadotropin
1932	Riddle Bates and Dykshorn ⁴⁵	Lactogenic hormone isolated
1933	Barnes, Regan and Bueno ⁵	Thyroid hormone antagonizes antidiuretic principle of posterior pituitary
1933	Collip Anderson and Thomson ¹¹	Adrenocorticotrophic hormone identified
1933	Cushing ¹⁶	Basophilic adenoma described in relation to Cushing's disease
1934	Collip and Anderson ¹²	Antihormone theory originated
1935	Fisher, Ingram and Ranson ²²	Water balance regulated by neurohormonal mechanism
1936	McConnell ³⁰	Diabetes insipidus favorably influenced by partial thyroidectomy
1937	Young ⁶⁶	Permanent diabetes produced in puppies by injections of anterior lobe extracts
1938	Sheehan and Murdock ⁵¹	Postpartum necrosis of anterior pituitary
1940	Various workers	Follicle stimulating and luteinizing hormones purified
1943	Marx, Simpson and Evans ³⁵	Growth hormone purified

II ANATOMY

A LOCATION

- 1 A reddish gray oval body attached to the brain by a stalk (infundibulum) which is continuous with the tuber cinereum¹
- 2 Pituitary gland protected by the sella turcica, lies
 - a Behind the optic chiasma
 - b In front of the corpora mammillaria
- 3 The pituitary fossa (sella turcica) is found in the middle cranial fossa just above the body of the sphenoid bone

B PARTS (nomenclature by International Commission on Anatomic Nomenclature⁵)

- 1 Adenohypophysis (see Fig 20)
 - a Lobus glandularis
 - (1) Pars distalis
 - (2) Pars tuberalis
 - (3) Pars intermedia
- 2 Neurohypophysis
 - a Lobus nervosus (neural lobe)
 - (1) Processus infundibuli

2 Arrangement

- a Cells within irregular cords are surrounded by
 - (1) Basilar sinuses
 - (2) Connective tissue

- ii Variable number of cells in each cord

- (1) Chromophils—most numerous
 - (2) Acidophils—outnumber basophils
 - (3) Walls of cord—usually 1 to 2 cells in thickness

- c "Colloid" masses often present in cell cords resembling true follicles

- d Peripheral cords

- (1) Basophils—mostly
 - (2) Chromophobes—few

- Central cords

- (1) Chromophobes—majority
 - (2) Acidophils—rare

3 Relationship

- a Chromophobes may become

- (1) Acidophils
 - (2) Basophils

- ii Chromophils may return to chromophobe state

- c Interchange between acidophil and basophil must take place through the chromophobe stage

- d Certain chromophobes develop only into a specific type of chromophil

4 Distribution

- a Average cellular percentages (both sexes)

- (1) Chromophil
 - (a) Acidophilic—37 per cent
 - (b) Basophilic—11 per cent
 - (2) Chromophobes—52 per cent

- b Both sexes with aging

- (1) Acidophils—decrease
 - (2) Chromophobes—increase

- c Males basophils are more numerous

- d Females basophilic number can increase

II INTERMEDIATE LOBE¹

- 1 A cellular remnant, often only a single layer of cells

- 2 Cells

- a Nongranular

- (1) Shape—polygonal
 - (2) Specific granules—absent
 - (3) Basic stain—pale
 - (4) Cilia may be present
 - (5) Follicular arrangement
 - (6) Lumen contains hyaline material

- ii Basophils

- (1) Smaller than those of anterior lobe
 - (2) Cellular prolongation into neural lobe

C POSTERIOR LOBE²⁰

1 Cells

- a Pituitary cells (neuroglia)

- (1) Shape

- (a) Fusiform
 - (b) Irregular

- (2) Granules

- (a) Present
 - (b) Absent

- (3) Processes

- (a) Long
 - (b) Branching

- (4) Nuclei

- (a) Distinct
 - (b) Granules of fine chromatin

- b Basophils (probably originate from intermediate lobe)

- (1) Size

- (a) Small
 - (b) Large

- (2) Increase with age

- 2 Hyaline bodies ("Herring bodies")

- 3 Connective tissue

- 4 Plexus of unmyelinated nerve fibers

D CONDITIONS WHICH ALTER THE PITUITARY CELLS (see 2 IV B)

- 1 Castration—physiologic or surgical (male or female)

- a General^{1,3 8 11 1 11 15-19}

- (1) Acidophils^{1,3 8 13 35 54 55}

- (a) These cells decrease slightly in

- [1] Number

- [2] Size

- [3] Staining capacity

- (b) Regress toward chromophobe state

- (2) Basophils

- (a) These increase in

- [1] Size

- [2] Number

- (b) Some of the basophils become vacuolated with a colloidlike material which displaces the nucleus giving the cells a "signet ring" appearance

- 4 The dorsal wall of Rathke's pouch, lying next to the posterior lobe and separated from the pars anterior by the cleft, forms the pars intermedia
- 5 The upper portion (pars tuberalis) of the pouch spreads around the pituitary stalk (infundibulum), which remains in contiguity with the third ventricle

B ORIGIN (see Fig 21)

- 1 Somatic ectoderm (primitive buccal cavity) gives rise to the pars
 - a Distalis
 - b Tuberalis
 - c Intermedia
- 2 Neural ectoderm (floor of third ventricle) produces the
 - a Pars nervosa
 - b Pituitary stalk

C TIME OF DEVELOPMENT (in weeks)

- 1 Five Rathke's pouch develops
- 2 Seven Both primordia lie in apposition
- 3 Eight Anterior lobe is within the sella turcica
- 4 Ten Pituitary gland well formed
- 5 Twelve Eosinophils
- 6 Sixteen Basophils
- 7 Twenty eight Chromophobes

IV CONGENITAL ANOMALIES

A ABSENT—Lethal cranial deformities, i.e. anencephaly

B APLASIA³

C TUMORS

- 1 Arise from embryonic cellular rests of hypophyseal (cranio-pharyngeal) duct, original connection of Rathke's pouch to the buccal cavity which may be called
 - a Craniopharyngioma
 - b Rathke's pouch cyst
 - c Suprasellar cyst
 - d Interpeduncular cyst
 - e Hypophyseal duct growth
- 2 Originate from other embryonic anlagen (rare)
 - a Dermoid cyst
 - b Teratoma
 - c Cholesteatoma
 - d Chordoma

D INTERPEDUNCULAR ANEURYSM

E ABERRANT TISSUE SITES

- 1 Pharynx¹
- 2 Floor of
 - a Third ventricle
 - b Sella turcica between dural layers
- 3 Sphenoid bone

V HISTOLOGY^{15 19}

A ANTERIOR LOBE (see Fig 22)

- 1 Types of cells
 - Chromophobes (neutrophils, chief reserve or clear)
 - (1) Shape
 - (a) Small
 - (b) Rounded
 - (c) Polyhedral
 - (2) Cytoplasm
 - (a) Diffuse
 - (b) Clear
 - (c) Light staining
 - (3) Granules
 - (a) Few
 - (b) Size variable
 - (4) Cell walls—inconspicuous
 - (5) Mitochondria
 - (6) Golgi apparatus
- b Chromophils (granular)—2 types
 - (1) Acidophils (eosinophils, oxyphils or alpha)
 - (a) Size larger than
 - [1] Chromophobes
 - [2] Basophils
 - (b) Shape
 - [1] Round
 - [2] Columnar
 - (c) Granules within cytoplasm
 - [1] Stainable with dyes acid or basic (certain ones)
 - [2] Grouped at one pole
 - [3] Scattered sometimes
 - (d) Cell walls distinct
 - (e) Mitochondria—numerous
 - (f) Golgi apparatus
 - (g) Nuclei
 - [1] Round
 - [2] Vesicular
 - [3] Chromatin scant
 - [4] Pyknotic occasionally
 - (2) Basophils (cyanophil beta)
 - (a) Granules take basic stain
 - (b) Essentially same cellular components as acidophils

2 Arrangement

- a. Cells within irregular cords are surrounded by
 - (1) Basilar sinuses
 - (2) Connective tissue
- b. Variable number of cells in each cord
 - (1) Chromophils—most numerous
 - (2) Acidophils—outnumber basophils
 - (3) Walls of cord—usually 1 to 2 cells in thickness
- c. Colloid masses often present in cell cords resembling true follicles
- d. Peripheral cords
 - (1) Basophils—mostly
 - (2) Chromophobes—few
- e. Central cords
 - (1) Chromophobes—majority
 - (2) Acidophils—rare

3 Relationship

- a. Chromophobes may become
 - (1) Acidophils
 - (2) Basophils
- b. Chromophils may return to chromophobe state
- c. Interchange between acidophil and basophil must take place through the chromophobe stage
- d. Certain chromophobes develop only into a specific type of chromophil

4 Distribution

- a. Average cellular percentages (both sexes)
 - (1) Chromophil
 - (a) Acidophilic—37 per cent
 - (b) Basophilic—11 per cent
 - (2) Chromophobes—52 per cent
- b. Both sexes with aging
 - (1) Acidophils—decrease
 - (2) Chromophobes—increase
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| 7 Twenty eight | Chromophobes |

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 - (g) Nuclei
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 - [3] Chromatin scant
 - [4] Pyknotic occasionally
 - (2) Basophils (cyanophil beta)
 - (a) Granules take basic stain
 - (b) Essentially same cellular components as acidophils

- (2) Gonadotropic hormones (GTH)
 - (a) Follicle stimulating hormone (FSH, seminiferous tubular stimulating, STSH, prol-in A, thy-lakentrin, gametokinetic)
 - (b) Luteinizing hormone (LH, prol-in B, metakentrin, interstitial cell stimulating ICSH)
 - (c) Luteotropic hormone
- (3) Thyrotropic hormone (TSH)
- (4) Adrenocorticotrophic hormone (corticotrophic, adrenotropic ACTH)
- (5) Diabetogenic hormone
- (6) Galactins
 - (a) Lactogenic hormone (prolactin)
 - (b) Mammogen I (?)
 - (c) Mammogen II (?)
- (7) Adrenomedullitropic hormone (?)
- (8) Parathyrotropic hormone (?)
- (9) Splenotropic principle (?)
- (10) Metabolic hormones
 - (a) Carbohydrate
 - [1] Pancreatropic factor (?)
 - [2] Contra insulin factor (?) (possibly the same as adrenocorticotropin)
 - [3] Glycotropic factor (?) (anti insulin factor)
 - [4] Glycostatic factor (?)
 - [5] Hyperglycemic factor (?)
 - [6] Insulotropic principle (?)
 - (b) Fat
 - [1] Ketogenic factor (?)
 - [2] Lipotropic factor (?)
 - (c) Protein metabolism factor (?)
 - (d) Water metabolism factor (?)
 - (e) Calcium factor (?)
- (11) Renotropic factor (?)
- (12) Hepatic and cardiac factors (?)
- (13) Hematopoietic factor (?)
- b Intermediate lobe
 - (1) Specific metabolic factor (?)
 - (2) Chromatophore stimulating factor (?) (melanophore erythrophore)
- c Posterior lobe
 - (1) Vasopressin
 - (2) Oxytocin
 - (3) Antidiuretic principle (?)
 - (4) Other factors (??)
 - (a) Lipotropic factor (?)
 - (b) Adrenalin inhibition factor (?)
 - (c) Hyperglycemic factor (?)
- 3 Growth hormone
 - a Its control is exerted directly and mainly on organism possibly the liver⁴² and not through other endocrine glands²¹
 - b Effectiveness in animals which are¹⁰
 - (1) Hypophysectomized
 - (2) Thyroidectomized⁴¹
 - (3) Thyroidectomized and hypophysectomized
 - (4) Adrenalectomized^{1, 34}
 - (5) Castrated¹⁰
 - (6) Pancreatized¹⁰
 - (7) Thymectomized⁴
 - c Protein metabolism—through anabolic action produces an increase in $\frac{10}{11} \frac{12}{13} \frac{14}{15} \frac{16}{17} \frac{18}{19} \frac{20}{21} \frac{22}{23} \frac{24}{25} \frac{26}{27} \frac{28}{29} \frac{30}{31} \frac{32}{33}$
 - (1) Growth rate of skeleton (immature animals)
 - (2) Appetite
 - (3) Food consumption
 - (4) Body weight^{9, 31}
 - (5) Muscle glycogen^{22, 43}
 - (6) Cartilage proliferation^{3, 10, 35, 43, 44}
 - (7) Weight of³⁷
 - (a) Thymus
 - (b) Lymph glands
 - (c) Liver (variable)
 - (8) Specific dynamic action¹⁸
 - d Carbohydrate metabolism
 - (1) Less conversion of protein to glucose in growing animals^{17, 21, 43}
 - (2) Initial hypoglycemia in adult rats is followed by hyperglycemic phase (anti insulin action)^{30, 40}

- (c) 'Castration' or "signet ring" cells do not develop in all species (rabbit or guinea pig)
 - (3) Cellular differentiation possible between (see 2 I \ B 14)
 - (a) Castration
 - (b) Thyroidectomy
 - b Males (after middle age)^{19 1}
 - (1) Pituitary weight decreases
 - (2) Cellular content
 - (a) Acidophils—decrease
 - (b) Basophils—no significant change
 - (c) Chromophobes—increase
 - c Female climacteric^{1 19 1}
 - (1) Hypophyseal weight remains the same
 - (2) Cellular content
 - (a) Acidophils—decrease
 - (b) Basophils—increase, then decrease
 - (c) Chromophobes—increase
 - (3) Secretory (gonadotropic) activity increases
 - 2 Pregnancy
 - a Pregnancy cells arise from chromophobes which may become^{6 7 12 18}
 - (1) Granulated
 - (2) Degranulated
 - b Acidophils and basophils^{4 8}
 - (1) Secrete very actively
 - (2) Degranulation of both types
 - (3) Golgi apparatus—hypertrophied
 - (4) Mitochondria—numerous
 - c Cellular findings indicate state of activity^{10 13 23}
 - (1) Acidophils increase in the following stages of pregnancy
 - (a) Early
 - (b) Full term
 - (c) Postpartum
 - (2) Basophils increase toward full term only
 - d Whole gland increases in^{7 9 14}
 - (1) Size
 - (2) Weight
 - a Role as the chief stimulator of bodily growth
 - b Hormonal dominance to a greater or lesser degree of other endocrine glands, through which most vital functions are controlled
- ## II INDIVIDUAL HORMONES
- ### 1 Introduction
- a Functions of the hormones are learned by
 - (1) Removal of the endocrine gland or glands
 - (2) Studies by replacement therapy
 - (3) Clinical observation on patients with the effects of hyposecretion or hypersecretion
 - (4) Production of an excessive amount by using
 - (a) Glandular extracts
 - (b) Isolated or synthetic compounds
 - b Dosage is important because giving the minimum may have the opposite effects of large amounts as demonstrated in various animals
 - c Since many preparations are not purified and because various hormones may be closely related there is obviously an overlapping in experimental results
 - d The species the diet and the environment of animals must be considered in evaluating the final conclusions
 - e The following are illustrative examples regarding the animal which may be used
 - (1) Normal (infantile or adult)
 - (2) Parabiologic
 - (3) Removal of the endocrine gland(s) either alone or plus another
 - f While deductions from animal studies may be projected into human physiology allowances always must be made for differences in species
 - g The criteria presented above apply to all hormones as discussed subsequently
- ### 2 List of hormones (principles factors)
- a Anterior lobe
 - (1) Growth hormone (somatotrophic)

VI FUNCTIONS

A GLAND AS A WHOLE

- 1 The primary functions of the pituitary are probably its

(1) Females (animals)

(a) I SH and minimal traces of LH stimulate^{8 1 11 12 25}

- [1] Ovarian weight
- [2] Estrogen secretion^{13 15}
^{27 28}
- [3] Progesterone formation
- [4] Ovulation (follicles must be in preovulatory stage)^{1 2 3 5 1 1-17 24 27}
- [5] Involution of persisting corpora lutea¹
- [6] Uterine growth (after ovarian effects)

(b) I SH and greater amounts of LH (same effects may be produced by inorganic salts or inert proteins combined with FSH¹⁹) cause follicular^{16 27}

- [1] Luteinization
- [2] Cystic degeneration

2) Males

(a) Testicular effects

- [1] Enlargement¹⁶
- [2] Descent (possibly only ICSH)^{14 22}
- [3] Spermatogenesis enhanced¹⁹

(b) Accessory organs increase in size, due to greater Leydig cell secretion^{22 23 24}

(3) Males and females (animals)

(a) Specific dynamic action of protein is not influenced (hypophysectomized rats)²³(b) Alkaline phosphatase (rats) is increased in epiphyses and diaphyses²³(c) Creatinine excretion is increased without affecting creatine²⁴(d) Cholesterol metabolism of the adrenal cortex is decreased after a preliminary rise (rats)⁴4) Luteotropic hormone^{9 10 20}

- (1) It may be same as lactogenic hormone
- (2) Corpora luteal function maintained

5 Thyrotropic hormone (TSH)

a Introduction

(1) Primary action of thyrotropic hormone (TSH) is upon thyroid cells^{4 7 16 18-21 1 32-37}

(2) In consequence there is an outpouring of thyroid hormone, which accounts for most of the physiologic changes following injection of TSH (These are described under hyperthyroidism, 14 VI B)

(3) However, certain effects are independent of the thyroid gland, since they may be produced in thyroidectomized animals

(4) Thyroid hormone on the other hand, is considered to have an inhibiting effect upon the

- (a) Thyrotropic hormone
- (b) Hypothalamus

b Effects of injection of TSH in normal or thyroidectomized animals

(1) Exophthalmos may be produced (also in castrated animals)^{1 2}
^{10 11 16 20 26 29 37 40 4 43}(2) Fat increased in^{10 11}

- (a) Blood
- (b) Liver
- (c) Muscles
- (d) Epithelial cells
- (e) Lymph nodes
- (f) Spleen
- (g) Kidneys
- (h) Polymorphonuclear leukocytes
- (i) Tissue macrophages
- (j) Thyroid cytoplasm

(3) Blood acetone increased

c Other effects are related to secondary increase of thyroid hormone secretion (see 14 VI B)^{3 8 9 1 15 17}
^{19 27 29 3 31 38 39-41 47 45 40 51}

6 Adrenocorticotrophic hormone (corticotrophic adrenotropic ACTH)

a Introduction (see 39 VI B I 2, 106 III E)

- (1) The action of adrenocorticotrophic hormone, or hormones is to stimulate the adrenal cortices^{15 25 32, 37 71}

- (3) Diabetes has been produced in
 - (a) Dogs (not puppies)^{4 5 8 48}
 - (b) Cats⁶
 - (c) Batrachians⁷³
- Alterations in tissue constituents
 - (1) Weight gain due to⁷
 - (a) Fat decrease
 - (b) Protein increase
 - (c) Water increase
 - (2) Liver
 - (a) Decrease in¹⁴
 - [1] Arginase
 - [2] Ribonucleic acid
 - (b) Increase in⁸
 - [1] Labile protein
 - [2] Fatty infiltration⁴³
 - (3) Thymus may have an increase in nucleic acid turnover
- f Respiratory quotient is decreased^{15 20 22 30}
- g Urinary excretion
 - (1) No change in
 - (a) Uric acid
 - (b) Creatinine
 - (2) Decrease in^{31 46}
 - (a) Nitrogen^{14 5 29 48}
 - (b) Phosphorus
 - (c) Sulfur, probably
 - (3) Calcium may be increased^{31 43 46}
- h Blood constituents
 - (1) Decrease in
 - (a) Nonprotein nitrogen^{18 47}
 - (b) Amino acids (urea nitrogen unchanged)^{1 15 39}
 - (2) Increase in
 - (a) Inorganic phosphorus⁶
 - (b) Alkaline phosphatase
- 4 Gonadotropic hormones^{12 55}
 - a Females (see 57 VI B 1 2)
 - (1) Follicle (or seminiferous tubular) stimulating hormone—FSH
 - (a) Stimulates^{1 1 4 35}
 - [1] Follicular development (antrum to preovulatory stage)
 - [2] Ovarian weight
 - [3] Estrogen secretion for secondary sex development, but probably not sexual hair
 - (b) No effect on
 - [1] Interstitial tissue
 - [2] Theca
 - (2) Luteinizing (or interstitial cell stimulating) hormone—LH or ICSH
 - (a) Stimulates
 - [1] Corpus luteum formation which in turn secretes progesterone^{1 15 18} (prolactin may or may not be necessary for this effect^{7 9 11 37})
 - [2] Interstitial cells
 - (b) Inhibits possibly
 - [1] Estrogen production and estrus
 - [2] The further development of follicles
 - b Males (see 45 VI B 1, 2)
 - (1) Seminiferous tubular stimulating (or follicle stimulating) hormone—STSH or FSH
 - (a) Stimulates^{8 19 20 23 25 31}
 - [1] Seminiferous tubules
 - [2] Spermatocytogenesis and spermatogenesis
 - [3] Testicular weight
 - (b) No effect on²²
 - [1] Accessory sex organs
 - [2] Leydig cells
 - [3] Nitrogen excretion (rats)³⁰
 - (2) Interstitial cell stimulating (or luteinizing) hormone—ICSH or LH
 - (a) Stimulates⁷⁸
 - [1] Interstitial Leydig cells of testes to secrete male sex hormone (testosterone) which in turn produces development of
 - [a] Accessory sex organs^{8 19 20 23}
 - [b] Seminiferous tubules
 - [2] Testicular weight
 - (b) Evidence for effect on adrenal cortex is not conclusive^{2 32}
 - c Follicle stimulating and luteinizing hormones act synergistically (it is doubtful if FSH can be prepared without traces of LH and vice versa)

(d) Pancreas

- [1] Insulin content increased (rats) to an average of 40 per cent above normal level²⁰
- [2] If removed severe protein breakdown and diabetes⁶¹

(10) Mammary glands—prolactin is aided in initiation of lactation^{70 49 4}

■ Effects due to so-called nitrogen retaining protein anabolic or "N" hormone are not clearly demonstrated with injections of ACTH, possibly because "S" hormones are dominant

d Results due to salt regulating or mineral hormones are not proved very well in experimental animals by injections of ACTH

e Effect of ACTH by injection in normal humans (see also 106 III E 3)
8 18 47 57

- (1) Comment — changes reported vary with different observers probably because of
 - (a) Dosage
 - (b) Purity of extract
 - (c) Conditions of experiment

- (2) Hematologic findings⁴⁷
 - (a) Hemoglobin decreased
 - (b) White blood cells^{18 70 57}
 - [1] Eosinophils decreased⁷³
 - [2] Lymphocytes decreased
 - [3] Polymorphonuclears increased
 - (c) Cell volume decreased

- (3) Urinary excretion
 - (a) No change in⁴⁷
 - [1] Gonadotropins
 - [2] Estrogens
 - [3] Pregnanediol
 - (b) Decrease in^{47 64}
 - [1] Creatinine (or no change)
 - [2] Creatine
 - (c) Increase in
 - [1] Sugar^{8 57}
 - [2] Total nitrogen (see 106 III E 3 f)^{8 18 9}
 - [3] Uric acid^{8 18 17 18}

- [4] Potassium (but variable)^{18 47 7}
- [5] Sodium (but variable)^{18 47}
- [6] Chloride (or decrease)^{18 57}
- [7] 17 Ketosteroids^{18 47 81}
- [8] Cortinlike substances^{18 47 81}
- [9] 11 oxysteroids^{18 47}
- [10] Androsterone⁴⁷
- [11] Etiocolanolone⁴⁷

(4) Blood chemical analyses

- (a) No change in⁴⁷
 - [1] Nonprotein nitrogen (blood)
 - [2] Uric acid (serum)
 - [3] Protein (plasma)⁷
 - [4] Globulin (serum)¹⁸
 - [5] Albumin globulin ratio
 - [6] Alkaline phosphatase (serum)

- (b) Decrease or no change in⁷
 - [1] Potassium (plasma)
 - [2] Phosphorus (serum)
 - [3] Glutathione⁸
- (c) Increase in peptidases (serum)⁵⁷

- (d) Increase or no change in^{47 49 7}
 - [1] Sugar (blood)^{18 7}
 - [2] Sodium (plasma)¹⁸
 - [3] Chloride (plasma)^{18 36 57}
 - [4] Carbon dioxide (plasma)¹⁸
- (e) Decrease in free cholesterol (plasma)⁴⁷

- (5) Tolerance tests⁴⁸
 - (a) Glucose^{8 47 57}
 - [1] Normal
 - [2] Diabetic
 - (b) Insulin — increased resistance⁷
- (6) Miscellaneous⁴⁷
 - (a) Acne
 - (b) Weight increase
 - (c) Pitting edema
 - (d) Blood pressure not affected⁵⁷

- (7) Changes observed in patients with various diseases parallel above findings (see 106 III E)

- (2) Cortical secretions may in turn have an inhibitory influence on the pituitary,^{9 7-} while epinephrine may release ACTH^{48 53}
 - (3) With the purification of ACTH near at hand, accumulating evidence suggests that most if not all, of the secretions of the adrenal cortices are under control of one rather than several pituitary adrenocorticotrophic factors
 - (4) However, it is doubtful if such a conclusion is possible
 - (5) The action of ACTH and the effects produced by secondary elaboration of adrenocortical hormones are enumerated here, because they cannot be individually assigned to isolated hormonal compounds of the cortex
 - (6) Several categories of function may be used to illustrate the results of ACTH injections
- b Effects due to so called sugar ('S carbohydrate or glucocorticoid) hormones in experimental animals¹
- (1) Carbohydrate metabolism^{30 36 37 40}
 - (a) Carbohydrate utilization retarded¹¹
 - (b) Glycogen deposition increased in
 - [1] Muscle^{28 38 39}
 - [2] Liver^{3 33 60}
 - (c) Gluconeogenesis^{8 38 39}
 - (d) Hyperglycemia^{11 60}
 - (e) Glycosuria^{25 38 60}
 - (f) Insulin resistance^{3 38 39}
 - (2) Fat metabolism—some deposition of fat⁴¹
 - (3) Protein metabolism
 - (a) Anti anabolic or excess catabolic action^{1 27}
 - (b) Negative nitrogen balance may be augmented by high protein intake^{1 6}
 - (c) Liver arginase activity increased^{19 21 23}
 - (d) Blood urea and nonprotein nitrogen increased⁴
 - (e) Specific dynamic action is not influenced (rats)⁻⁵
 - (4) Lymphoid tissue^{6 10 13 14 45 60 70}
 - (a) Dissolution of tissue in
 - [1] Thymus^{38 60}
 - [2] Lymph glands^{5 1}
 - (b) Serum globulins, beta and gamma^{9 38 77 79}
 - [1] Increased consequently
 - [2] Important in antibody formation
 - (c) Circulating white blood cells
 - [1] Lymphocytes decreased^{11 12 14 31 64 79 80}
 - [2] Eosinophils decreased³³
 - [3] Polymorphonuclears increased^{11 12 31 61 78 80}
 - (d) Splenin—a hormonal substance released from the spleen (?)³
 - (e) Resistance to stress increased^{14 38}
 - (5) Bleeding time may be decreased
 - (6) Circulating red blood cells are increased then eventually decreased^{11 60 78 79}
 - (7) Renal function may be impaired^{3 5 67 68}
 - (8) Growth retardation and decreased^{4 6 16 33 48 60 78}
 - (a) Chondrogenesis
 - (b) Osteogenesis
 - (c) Alkaline phosphatase (serum)⁴³
 - (d) Osteoblastic activity³⁴
 - (9) Endocrine glands
 - (a) Thyroid⁴²
 - [1] Weight—decreased
 - [2] Hypoplasia—produced
 - (b) Adrenal cortices show depletion of
 - [1] Cholesterol^{7 60 63 74}
 - [2] Ascorbic acid⁶¹
 - (c) Testes and accessory sex organs^{4- 74}
 - [1] Atrophy (normal or hypophysectomized rats)
 - [2] Prostate (ventral) increased (hypophysectomized rats)⁷⁴

- (7) Basal metabolic rate increased (thyroidectomized pigeons)²¹
- b Mammogen I—stimulates duct growth (animal experiments)^{1 2 3 11 17}
- c Mammogen II—causes lobulo alveolar growth (may be same as lactogenic hormone) (animal experiments)^{4 11 20 22}
- 9 Adrenomedullotropic principle (?)—"dark cells" of adrenal medulla stimulated without change in chromaffin tissue (hypophysectomized rats)^{1 3}
- 10 Parathyrotropic hormone (?)^{1 4 5}
- a Parathyroid activity may be increased without change in size as shown by
- (1) Hyperemia
 - (2) Histologic findings
- b Hypercalcemia occurs but results are variable^{2 6}
- 11 Splenotropic principle (?)¹
- a Evidence is not sufficient to distinguish this principle from growth hormone
- b Splenic size may be increased
- 12 Metabolic factors
- a Carbohydrate metabolism factors
- (1) Pancreatotropic factor (?)^{2 23 27 28, 29, 30}
 - (a) Probably its effects are produced indirectly through action of glycotropic or diabetogenic factors
 - (b) Stimulation of
 - [1] Islet cells to increase in^{7 21 22}
 - [a] Number
 - [b] Size
 - [c] Insulin production
 - [2] Protein anabolism^{9 25 31 47}
 - [3] Nitrogen retention
 - [4] Body weight gain
 - (c) Blood sugar level decreases usually
 - (2) Contra insular factor (?)
 - (a) Identical with ACTH possibly
- (b) Blood sugar increases when this factor is injected suboccipitally into cerebrospinal fluid (seems to act through the adrenal cortex)
- (3) Glycotropic (anti insulin) factor (?)
- (a) Same as ACTH probably²³
 - (b) Anti insulin effect is produced through stimulation of adrenal cortex²³
 - (c) Blood sugar is not converted into muscle or liver glycogen (opposite to insulin effect)^{6 11 17 18 20 22 30 45 46}
 - (d) It may not be identical with^{45 46}
 - [1] Gonadotropin
 - [2] Thyrotropin
 - [3] Prolactin
 - [4] Ketogenic factor
 - [5] Melanophore stimulating factor
- (4) Glycostatic factor (?)^{11 14 16, 29 40}
- (a) Glycogen storage is increased in
 - [1] Liver
 - [2] Muscles
 - (b) Hyperglycemia in well fed animals
 - (c) Protein catabolism reduced, producing hypoglycemia amino acids here are only source of carbohydrates in normal fasted rats
- (5) Hyperglycemic factor (?)—liver glycogenolysis occurs with subsequent rise in blood sugar
- (6) Insulotropic principle (?)—insulin producing cells of islets of Langerhans are stimulated directly¹
- b Fat metabolism factors
- (1) Ketogenic factor (orophysin) (?)^{1 4 8-10 41}
 - (a) May be identical with
 - [1] Growth hormone
 - [2] Diabetogenic factor
 - (b) Is found in preparations of
 - [1] Growth hormone
 - [2] Thyrotropin
 - [3] Prolactin

7 Diabetogenic principle

a Introduction

- (1) Diabetogenic effects in the past have been produced largely from crude extracts
- (2) Factors causing diabetes in such extracts have been considered in part due to^{1 5 8 12 16}
 - (a) Growth hormone^{1 16}
 - (b) Thyrotropin
 - (c) Adrenocorticotropin
 - (d) Prolactin
- (3) Purified growth hormone will produce diabetes in
 - (a) Dogs (not puppies)
 - (b) Cats
 - (c) Batrachians

b Carbohydrate metabolism

- (1) Blood sugar increased^{2 3 5 7 9 1 16}
- (2) Liver glycogen maintained⁵
- (3) Carbohydrate utilization inhibited
- (4) Glycosuria produced^{4 5 8 12 15 16}
- (5) Ketonuria (moderate or none)^{4 5 9-1 15 16}

c Fat metabolism

- (1) Production of⁵
 - (a) Hyperlipemia
 - (b) Hypercholesterolemia
- (2) Oxidation of stored fat increased¹⁶

d Protein metabolism⁵

- (1) Plasma protein level may rise
- (2) Body protein deposition increased
- (3) Nitrogen retention enhanced by the secretory activity of the islets of Langerhans

e Growth accelerated (see above) in puppies causing^{14 16}

- (1) No diabetes with brief trials
- (2) Diabetes in long experiments (and growth cessation eventually)

f Body weight increases^{9-13 16}g Metabolic rate normal¹⁶

h Respiratory quotient lowered (dogs, cats, rats, rabbits)

i Hematinic glutathione increased⁵8 Galactins (animal experiments)^{20 25-30}
3 11 11 30

a Lactogenic hormone (prolactin)

- (1) Mammary glands stimulated
 - (a) Milk secretion (ACTH is probably essential)^{11 14}
 - [1] Initiated
 - [2] Maintained
 - (b) Lobulo alveolar growth may be produced
- (2) Effects on reproductive processes
 - (a) Progesterone formation may (or may not) be dependent on prolactin (questionable in normals)^{1 7 10 13 37}
 - (b) FSH inhibited (birds, rats)
 - (c) Estrus cycle depressed (rats, mice, doves)^{3 6 10 13}
 - (d) Pregnancy³⁴
 - [1] Span may be prolonged (rodents)
 - [2] Prevention by excessive delay in implantation (rodents)
 - (e) Pseudopregnancy can be induced (rats)¹⁹
 - [1] Follicles do not mature
 - [2] Ovulation inhibited
 - [3] Vagina shows high degree of cornification
 - [4] Endometrium has progestational changes
 - [5] Hypertrophic corpora lutea secrete progesterone
 - [6] Mammary glands show lobulo alveolar development¹⁰
 - (f) Sexual behavior³⁸
 - [1] Nesting behavior (fish)
 - [2] Parental instincts (rats)
 - [3] Brooding (fowls)
- (3) Splanchnomegaly (pigeons) of^{7 8 30}
 - (a) Liver
 - (b) Pancreas
 - (c) Intestine
- (4) Growth not affected^{18 3}
- (5) Nitrogen excretion unaltered (rats)^{18 21}
- (6) Blood sugar not increased in dogs³⁶

(c) Thyroidectomized

(d) Adrenalectomized

(7) Exophthalmos = not produced⁴

b Decreases

(1) Carbohydrate oxidation

(2) Insulin sensitivity

(3) Hyperglycemia of adrenalin

(4) Respiratory quotient

(5) Nitrogen retention

c Increases

(1) Basal metabolic rate independent of the thyroid gland (humans rabbits rats guinea pigs)

(2) Oxygen consumption (humans animals—fasted or fed)

(3) Carbon dioxide production especially in fasted animals

(4) Body temperature

(5) Gluconeogenesis (possibly)

(6) Glycosuria and ketonuria (Hous-
say dogs)

(7) Glycostatic action (rats guinea
pigs, rabbits)

(8) Fat metabolism

(9) Ketonemia (fasted rats)

17 Chromatophore stimulating or expanding factor (?) (melanophore erythro-
phore)^{1 2 17 20-22}

a Comment

(1) Although the presence of this factor in humans has not been demonstrated it probably exists in all other vertebrates either singly or as a part of another hormone

(2) Each name above refers to the specific type of pigment cell that responds to stimulation by the factor

b Pigmentation is controlled by

(1) Melanophore stimulating factor which produces darkening of the animal by dispersion of melanin granules (melanosomes) in pigment cells (melanophores) of lower vertebrates as^{1 5 8 1 13 15 17 20 22}

(a) Fish (specific types)

(b) Amphibia

(c) Reptiles

(2) Erythrophore stimulating factor expands the red granules (erythrosomes) of pigment cells (erythrophores) in certain fish

c Formation of new melanin (questionable)^{2 11}

d Adaptation to darkness by retinal pigment cells = accelerated⁴

e Body temperature may be increased (rabbits)¹⁰

f Adrenal cortical hypertrophy (rabbits, rats guinea pigs)^{9 11}

g Hyperglycemia may occur (rabbits)¹⁰

h No effect on¹⁰

(1) Blood pressure

(2) Basal metabolic rate

(3) Liver glycogen

i Water excretion—variable results^{13, 19}

18 Vasopressin

a Comment

(1) The postulated principles of the posterior lobe have not been purified sufficiently to permit accurate analysis of their specific actions

(2) Many factors are involved in the results obtained as

(a) Species of animal

(b) Concentration of material

(c) Duration of experiment

(3) A single protein hormone may contain all three factors

b Smooth muscle^{16 21 27 33 37 41 45 2, 46}

(1) Small and large bowel activity is increased, but inhibition of movements in some portions may occur (variable reports)

(2) Defecation is aided

(3) Gastric motility = decreased

(4) Gallbladder is contracted (depends on its physiologic state)

(5) Bronchi are stimulated (not a specific action probably due to contamination)

(6) Uterus is stimulated^{43 47}

(a) Response according to physiologic state

(b) Most effective in nonpregnant uterus or early pregnancy

(7) Blood vessels are constricted

- (c) Decreases basal metabolic rate
- (d) Increases
 - [1] Output of acetone bodies in blood and urine after diet of butter fat or by fasting, rather than decreased utilization
 - [2] Liver fat deposition
 - [3] Fat catabolism beyond oxidation capacity of body (may be secondary effect) compensating for decreased protein catabolism²⁰
 - [4] Specific dynamic action of protein
- (2) Lipotropic factor (?)³⁴
 - (a) Origin from posterior lobe possibly
 - (b) Blood fat lowered (may be related to TSH)
 - (c) Liver fat is dependent on supply of hormone
 - [1] Decreased by large quantities
 - [2] Increased by moderate amounts
 - (d) Ketogenic factor probably counterbalanced by it
- c Protein metabolism factor (?)¹⁰⁻⁴
 - (1) Identical with growth factor possibly³⁻⁵
 - (2) Nitrogen excretion decreased
 - (3) Liver protein (alkaline soluble) decreased in 35 to 53 per cent of normal guinea pigs
 - (4) Regulation of blood amino acids
- d Water metabolism factor (?) has a diuretic action^{12 15 33 37 39 42}
 - (1) Thyroid gland is necessary for this function⁴³
 - (2) Antidiuretic factor of posterior lobe neutralizes it
- Calcium factor (?) regulates the calcium level, but the parathyroids must be present (see 2 VI B 10)
- 13 Renotropic factor (?)
 - a Kidney tissue atrophy may be prevented (following unilateral ligation of ureters in female rats)^{1 2}
 - b Renal tubular cells show
 - (1) Hyperplasia
 - (2) Hypertrophy
 - c Glomerular size increased
 - d Note that
 - (1) Thyroxin acts as a synergist⁴
 - (2) Thyroidectomy is antagonistic to these effects⁵
- 14 Hepatic and cardiac factors (?)¹
 - a These are considered independent of growth hormone
 - b Liver and heart have disproportional hypertrophy in comparison with bodily enlargement (bones, muscles)
- 15 Hematopoietic factor (?)^{1 2}
 - a Same as ACTH possibly
 - b Action may be
 - (1) Directly on bone marrow
 - (2) Indirectly on
 - (a) Thyroid
 - (b) Adrenals
 - (c) Testes
 - Hemoglobin is decreased
 - d Red blood cells and reticulocytes are increased
- 16 Specific metabolic factor (?)^{1 7 9 18}
 - a Comment
 - (1) Its presence has been demonstrated in most species (although doubtful in humans) by simple extracts of
 - (a) Pituitary tissue
 - (b) Dissected anterior or posterior lobes
 - (2) Concentration is greatest in
 - (a) Pituitary colloid
 - (b) Intermediate lobe
 - (3) Separation from the melanophore stimulating (expanding) hormone has not yet been successful
 - (4) Ketogenic and adrenalin inhibition factors are not identical with it
 - (5) All animals do not react to this principle and others show no resistance to repeated injections
 - (6) Specific actions although not clearly defined, have been demonstrated in animals that are
 - (a) Normal
 - (b) Hypophysectomized

- (c) Thyroidectomized
- (d) Adrenalectomized
- (7) Exophthalmos is not produced¹
- b Decreases
 - (1) Carbohydrate oxidation
 - (2) Insulin sensitivity
 - (3) Hyperglycemia of adrenalin
 - (4) Respiratory quotient
 - (5) Nitrogen retention
- c Increases
 - (1) Basal metabolic rate independent of the thyroid gland (humans rabbits, rats guinea pigs)
 - (2) Oxygen consumption (humans, animals—fasted or fed)
 - (3) Carbon dioxide production, especially in fasted animals
 - (4) Body temperature
 - (5) Gluconeogenesis (possibly)
 - (6) Glycosuria and ketonuria (Housay dogs)
 - (7) Glycostatic action (rats guinea pigs rabbits)
 - (8) Fat metabolism
 - (9) Ketonemia (fasted rats)
- 17 Chromatophore stimulating or expanding factor (?) (melanophore erythrophore)^{1 7 17 20 22}
 - a Comment
 - (1) Although the presence of this factor in humans has not been demonstrated, it probably exists in all other vertebrates either singly or as a part of another hormone
 - (2) Each name above refers to the specific type of pigment cell that responds to stimulation by the factor
 - b Pigmentation is controlled by
 - (1) Melanophore stimulating factor which produces darkening of the animal by dispersion of melanin granules (melanosomes) in pigment cells (melanophores) of lower vertebrates as^{1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100}
 - (a) Fish (specific types)
 - (b) Amphibia
 - (c) Reptiles
 - (2) Erythrophore stimulating factor expands the red granules (erythrosomes) of pigment cells (erythrophores) in certain fish
- c Formation of new melanin (questionable)^{3 14}
- d Adaptation to darkness by retinal pigment cells is accelerated⁴
- e Body temperature may be increased (rabbits)¹⁰
- f Adrenal cortical hypertrophy (rabbits rats, guinea pigs)^{9 11}
- g Hyperglycemia may occur (rabbits)¹⁰
- h No effect on¹⁰
 - (1) Blood pressure
 - (2) Basal metabolic rate
 - (3) Liver glycogen
- 1 Water excretion—variable results^{18 19}
- 18 Vasopressin
 - a Comment
 - (1) The postulated principles of the posterior lobe have not been purified sufficiently to permit accurate analysis of their specific actions
 - (2) Many factors are involved in the results obtained as
 - (a) Species of animal
 - (b) Concentration of material
 - (c) Duration of experiment
 - (3) A single protein hormone may contain all three factors
 - b Smooth muscle^{1 1 7 11 37 41 43 45 46 48 49}
 - (1) Small and large bowel activity is increased, but inhibition of movements in some portions may occur (variable reports)
 - (2) Defecation is aided
 - (3) Gastric motility is decreased
 - (4) Gallbladder is contracted (depends on its physiologic state)
 - (5) Bronchi are stimulated (not a specific action probably due to contamination)
 - (6) Uterus is stimulated^{13 47}
 - (a) Response according to physiologic state
 - (b) Most effective in nonpregnant uterus or early pregnancy
 - (7) Blood vessels are constricted

- c Cardiovascular
- (1) Muscle fibers of blood vessels contracted directly^{16 5}
 - (2) Blood pressure
 - (a) Rise, if any, is insignificant (no effect in normal humans)^{47 6}
 - (b) Momentary drop is produced by a decreased coronary blood flow
 - (3) The following are increased, after a temporary fall^{4 46}
 - (a) Pulse rate
 - (b) Cardiac output
 - (c) Oxygen consumption
- d Respiration^{1 19 23 9}
- (1) Acceleration usually
 - (2) Periods of apnea may be due to secondary circulatory effects on the respiratory center
- e Kidneys (see 2 VI B 20)
- (1) Urinary volume markedly reduced in normal individuals with high water intake by absorption at^{4 8 10 21 19 40 42 49 50 53 60 11}
 - (a) Proximal convoluted tubule
 - (b) Thin portion of Henle's loop (see 8 VI)
 - (2) Tubular chloride reabsorption remains the same^{10 15 40}
 - (3) Glomerular filtration rate increased¹⁰
 - (4) Plasma flow maintained effectively
 - (5) Water center (questionable) in hypothalamus inhibited (see 8 VI C 6)⁴⁸
 - (6) Glycosuria may occur in certain species^{3 17 28 11 34 62 6}
- f Gastrointestinal secretions inhibited^{6 30 5 57 58}
- g Central nervous system³⁸
- (1) Autonomic centers adjacent to ventricles stimulated
 - (2) Marked vasodilation may be produced at blush area with an injection into cerebral ventricles (man monkey)
- h Blood
- (1) Leukocytes increased¹¹
 - (2) Coagulation prolonged (questionable)⁹
- (3) Dilution causes a decrease in^{2 66}
 - (a) Hematocrit
 - (b) Specific gravity
 - (4) Hyperglycemia produced in certain species (an unidentified principle may cause this action)^{13 18 3 35 41 11}
 - (a) Antagonistic to insulin and epinephrine^{5 7 1 13 31 6}
 - (b) Glycotropic effect by formation of glycogen from carbohydrate sources (fasted rats, guinea pigs rabbits very little action in mice)¹
 - (5) Protein (serum) decreased⁶⁶
 - (6) Phosphate (inorganic, serum) elevated¹⁷
 - (7) Lipid substances show no significant changes^{30 54}
- 19 Oxytocin
- a Smooth muscle (variable results, dosage and method of administration important)
- (1) Intestine (large) shows inhibition of^{13 14}
 - (a) Tone
 - (b) Peristalsis
 - (2) Uterus^{1 7 11 13 16 19}
 - (a) Stimulation by direct action on myometrium
 - [1] Maximal effect (variable results) at parturition
 - [2] Slight change during first half of menstrual cycle
 - [3] All portions are not affected simultaneously
 - (b) Small amounts of principle
 - [1] Muscular tone augmented
 - [2] Amplitude of contractions increased
 - (c) Large amounts of principle may produce tetany (not in rabbits dogs)
- b Kidneys^{3 6 1*}
- (1) Excretion
 - (a) Creatine decreased
 - (b) Phosphate (inorganic) decreased
 - (c) Chloride increased

- (2) Glomerular filtration rate increased
- (3) Plasma flow increased
- Hyperglycemia ■ produced in certain species which may or may not be antagonistic to insulin action⁴ 6
8-10 11 70
- d Secretion of milk is increased in lactating animals (humans, too but of no clinical value)¹⁷
- Oxygen consumption slightly decreased
- 20 Antidiuretic principle (?) (may be a part of pitressin⁴)
 - a Water metabolism regulated¹ 3 6
■
 - (1) Action directly on descending loop of Henle
 - (2) Control of reabsorption of chlorides
 - b Salt and water balance controlled (not definitely established a relationship exists between posterior lobe and adrenals)² 7 13
- 21 Other posterior lobe principles (questionable)
 - a Lipotrin (?)—origin not confirmed (see 2 VI B 2 and 12)
 - b Adrenalin inhibition factor (?)¹⁻⁵
 - (1) Separate factor
 - (2) Epinephrine action may be inhibited
 - c Hyperglycemic factor (?) (certain species only)
 - (1) Insulin antagonism
 - (2) Glycotropic effect
- C HYPOPHYSECTOMY (see 2 VI)⁴⁴⁻⁴⁹ 1 6
 - 1 Introduction
 - a Literature on the removal of the pituitary gland is contradictory and confusing
 - b The results are often due to brain injury rather than the hypophysectomy
 - Other factors regarding the animal must be considered in each experiment as
 - (1) Species
 - (2) Age
 - (3) Care
 - (4) Diet
 - d Many survive for several months and demonstrate that the pars glandularis is the most essential portion of the mammalian pituitary
 - 2 All body and skeletal development particularly ceases in young animals¹ 29
81 8 118
 - 3 Atrophy of most glands and organs⁴ 11
20 11 11 113 119-121
 - a Thyroid² 9 22
 - (1) Greater iodine and thyroxine iodine content than in normal or partially hypophysectomized (dogs)
 - (2) Basal metabolic rate decreased (dogs rats and toads)
 - b Parathyroids (variable reports)⁵ 16
19 62 67 119-121
 - c Adrenals⁴ 16 60-62 95 117
 - (1) Cortical
 - (a) Atrophy
 - (b) Will not hypertrophy even under stress⁶⁴ 11 113
 - (2) Medulla unaffected
 - d Gonads and accessory reproductive organs are affected¹⁵ 63 but ripening and segmentation of ovum may take place (rats)⁷⁰ 134
 - e Pancreas
 - (1) Islets of Langerhans hypertrophy¹ 5
 - (2) Beta cells are
 - (a) Normal
 - (b) Hyperactive
 - (3) Weight is
 - (a) Normal
 - (b) Decreased³¹ 68
 - f Pineal unchanged
 - g Liver
 - h Spleen 8 90 90 127
 - 1 Viscera (small), except kidneys³¹
 - j Lymphoid tissue
 - (1) Thymus—variable data, atrophy may be an indirect effect from surgical shock⁵ 63 90 100 127
 - (2) No involution in rats¹¹² 214
 - k Bone marrow
 - (1) Hypoplastic usually
 - (2) White blood cell formation ■ not greatly impaired
 - 4 Hematologic findings
 - a Red blood cells decreased⁴ 61 70 127
 - b Anemia absent (rats)

- White blood cells^{24 89}
 - (1) No change
 - (2) Leukopenia slight, with eosinophilia
- d Color index increased (questionable if a, b, c and d are due to hypophysectomy alone)
- Reticulocytes decreased usually^{88 89}
77 17
- f Response to bleeding similar to normal rats with an increase in³⁰
 - (1) Red blood cells
 - (2) Hemoglobin
 - (3) Reticulocytes
- 5 Urinary excretion
 - Decreased
 - (1) Nitrogen, results variable (dogs rats, toads)^{71 74}
 - (2) Uric acid (dogs, rats on ordinary or nitrogen free diet)
 - (3) Creatinine (dogs rats)¹
 - (4) Purine bases (dogs rats on ordinary or nitrogen free diet)
 - (5) Ketones (dogs)⁸⁸
 - (6) Chlorides (rats)
 - b Increased (rats)
 - (1) Sodium
 - (2) Potassium
 - (3) Calcium
 - c Urobilin normal (dogs)
 - d Polyuria produced (dogs, rats, toads)
 - e Diuretic response to water is delayed (rats)⁶⁰
 - f Clearance tests (inulin diodrast) (dogs)^{130 131}
 - (1) Fifty per cent or more reduction
 - (2) Results indicate a decrease in
 - (a) Tubular activity
 - (b) Renal blood flow
- 6 Blood chemical analyses
 - a Potassium (plasma) (dogs)^{38 76 77}
 - (1) Normal
 - (2) Decreased (amphibia)
 - b Calcium
 - (1) Variable reports (toads dogs rats)^{1 37 43 59 69 77 96 116}
 - (2) No change probably in humans
 - Phosphorus, inorganic (dogs)^{58 66}
76 77
 - (1) Normal
 - (2) Decreased
 - d Iodine (protein bound) decreased⁹
14
 - (1) Fifty per cent decrease in rats by the third day
 - (2) Initial rise and then a fall in dogs due to change from hyperthyroid to ■ hypofunctional state
 - Phosphatase (serum) (dogs)^{37 38}
66 67
 - (1) Normal
 - (2) Decreased
 - f Magnesium (dogs)^{38 76 77}
 - (1) Normal
 - (2) Decreased
 - g Fatty acids total fats and cholesterol (dogs)^{84 110}
 - (1) Decreased
 - (2) Increased (rats)
 - h Amylase activity increased (dogs)²¹
 - i No change in the following (dogs)³⁸
76 77
 - (1) Nonprotein nitrogen
 - (2) Sodium
 - (3) Chlorides
 - (4) Carbon dioxide
- 7 Fecal excretion
 - a Decreased chlorides (rats)
 - b Increased
 - (1) Calcium
 - (2) Phosphorus
- 8 Carbohydrate metabolism
 - a Carbohydrate absorption from intestine may be altered due to secondary hypothyroidism⁹⁴
 - (1) Normal (toads)^{5 7}
 - (2) Decreased (rats) ■ 108
 - b Pancreas
 - (1) Normal amounts of insulin produced—variable reports^{40 41 ■}
58 1.3
 - (2) If rat ■ well fed, insulin content of pancreas is normal¹
 - c Diabetes (experimental) may be lessened by removal of pancreas
 - d Insulin sensitivity becomes extreme
23 36 59 133
 - Muscle glycogen^{23 106}
 - (1) Normal
 - (2) Decreased
 - f Liver glycogen^{6 73 105}
 - (1) Content
 - (a) Normal
 - (b) Decreased²⁵

- (2) No liberation as glucose into blood stream
- (3) Mobilization impaired by secreted adrenalin^{10 11}
- g Peripheral oxidation of carbohydrates is accelerated but is not due to^{103 104}
 - (1) Increased deposition of muscle glycogen
 - (2) Lactic acid production
- h Blood sugar is normal on an adequate diet, otherwise subnormal^{105 113}
- i Glucose tolerance tests¹⁰⁷
 - (1) Oral—generally increased
 - (2) Intravenous⁷
 - (a) Normal
 - (b) Decreased (rats)
- j Epinephrine effects less pronounced variable results
- k Gluconeogenesis from proteins is decreased⁶
- 9 Fat metabolism
 - a Cachexia may be
 - (1) Produced partly from fat loss in majority of animals
 - (2) Variable depending on experimental animal and diet
 - b Slight change in dogs
 - (1) Total fats
 - (2) Fatty acids
 - (3) Cholesterol
 - c Ketonuria decreased (dogs)
- 10 Protein metabolism
 - a Endogenous source^{13 13}
 - (1) Catabolism decreased
 - (2) Storage decreased in
 - (a) Liver
 - (b) Muscles
 - b Exogenous supply^{71 82, 109 111}
 - (1) Metabolism increased
 - (2) Storage decreased
 - c Specific dynamic action
 - (1) Increased relatively because of lowered basal metabolic rate (dogs)^{1 3 33 9}
 - (2) Decreased (rats)³²
 - d Globulins (plasma) increased (dogs)^{7 81}
 - e Albumin (plasma) increased (dogs rats)⁸³
 - f Viscosity (plasma) increased (dogs)
 - g Liver arginase activity decreased³³
- 11 General effects
 - a Glutathione decreased in
 - (1) Red blood cells
 - (2) Liver⁷³
 - (3) Muscles
 - b Muscular
 - (1) Activity subnormal
 - (2) Phosphocreatin decreased (toads 33%)
 - c Sensitivity increased to^{90 91}
 - (1) Infection
 - (2) Trauma
 - d Blood pressure^{93 113}
 - (1) Markedly lowered
 - (2) More sensitive (rats) to renin than normal or adrenalectomized animals
 - e Lactation inhibited^{94 83}
 - f Cutaneous pallor (animals) due to^{1 113}
 - (1) Contraction of melanophores
 - (2) Expansion of xanthophores
- 12 Observations with fasting and various diets
 - a Fasting
 - (1) Blood sugar^{39 7 83}
 - (a) Very low
 - (b) Hypoglycemia reactions of ten, may be fatal
 - (2) Glycogen decreased in^{74 101 106}
 - (a) Liver
 - (b) Muscles
 - (3) Gluconeogenesis from protein decreased
 - (4) Decreased excretion of
 - (a) Nitrogen (dogs^{13 14} toads⁵ rats¹)
 - (b) Creatinine (marked)
 - (c) Phosphate
 - b Protein free diet
 - (1) Decreased excretion of
 - (a) Uric acid
 - (b) Creatinine (marked)
 - (c) Purine bases
 - (d) Phosphate
 - (2) Protein catabolism decreased (dogs)
 - c Meat diet
 - (1) Nitrogen elimination normal/kg/day (dogs rats)
 - (2) Phosphate excretion normal
 - (3) Creatinine output slightly increased (dogs, rats)^{13 11}

- 13 Vitamin C content (male and female rats) is decreased in¹²⁵
- a Adrenals
 - b Testes
 - Liver
 - d Kidneys
 - Serum
- 14 Pregnancy
- Early
 - (1) Abortion
 - (2) Fetal resorption
 - b Late
 - (1) Period of gestation unchanged
 - (2) Stillbirth usually
 - c Parturition
 - (1) Normal
 - (2) Milk secretion slight after delivery
 - d Postpartum lactation stops
- 15 Hypophysectomy plus pancreatectomy (Houssay animal)^{40 50 53 55 60 133}
- a Excretion effects
 - (1) Polyuria
 - (a) Decreased
 - (b) Absent
 - (2) Glycosuria
 - (a) Decreased
 - (b) Absent
 - (3) Nitrogen does not show usual increase
 - b Blood chemical analyses
 - (1) Amylase activity normal (dogs)^a
 - (2) Decreased
 - {a} Sugar (animals may die of hypoglycemia shock)
 - (b) Cholesterol
 - (c) Sodium
 - (d) Potassium
 - (e) Calcium
 - (f) Chlorides
 - (g) Total lipids
 - (3) Alkaline reserve
 - (a) Normal
 - (b) Decreased
 - (4) Ketone bodies
 - (a) Small quantities
 - (b) Absent
 - c Carbohydrate metabolism
 - (1) Glucose tolerance curve usually quite low
 - (2) Carbohydrate produced by glyconeogenesis is utilized
 - (3) Respiratory quotient may increase after ingestion of glucose
 - (4) Glycogen is normal in
 - (a) Liver
 - (b) Muscles
 - (5) Insulin causes
 - (a) Extreme hypoglycemia
 - (b) Decreased life expectancy
- d Protein catabolism is slightly increased
- e Basal metabolic rate is not raised
- f Parathyroids degenerate
- Susceptibility to infection decreases
- h Wounds heal more rapidly
- i Comparison with ■ hypophysectomized animal shows that
- (1) Survival period is increased
 - (2) Weight loss occurs more slowly
- 16 Hypophysectomy plus thyroidectomy
- a Liver demonstrates all degrees of cirrhosis even on adequate diets (dogs) (see 2 VI C 11, VIII B 1c)¹⁷
 - b Lipid concentration (dogs) of the following (thyroid deficiency alone will do the same) is increased^{17 20 7}
 - (1) Total fatty acids
 - (2) Phospholipids
 - (3) Cholesterol (free and esterified)
 - c Vitamin C of adrenals ■ decreased as with hypophysectomy alone¹⁰⁰
- 17 Hypophysectomy plus splenectomy
- a Red blood cells increase⁸
 - b Hemoglobin increases
 - c Leukocyte count is unchanged²⁶
 - d Reticulocytes decrease⁷⁹
- D HYPERHORMONAL EFFECTS (see 2 VI)
- 1 On various organs and functions are summarized under
- a Individual hormones
 - b Gigantism
 - c Acromegaly
 - d Cushing's syndrome
 - e Pituitary and chorionic hormones
 - f Diabetes mellitus
- 2 On other endocrine glands
- a Growth hormone¹
 - (1) Thyroid
 - (a) Size—increased
 - (b) Hyperplasia—absent
 - (2) Parathyroids—possible increase in size

- (3) Adrenals (entire)—no change (rats)
- (4) Pancreatic islets
 - (a) No change (puppies)
 - (b) Diabetes (adult dogs)
- (5) Testes—no change (rats)
- (6) Ovaries—no change (rats)
- b Follicle stimulating hormone
 - (1) Increase in weight of
 - (a) Testes
 - (b) Ovaries
 - (2) Other glands—no data
- c Luteinizing hormone
 - (1) Testes—Leydig cell hyperplasia (see 2 VI B 4)
 - (2) Ovaries—luteinization (see 2 VI B 4)
 - (3) Other glands—no data
- d Thyrotropin
 - (1) Thyroid—hyperplasia
 - (2) Other glands—no data
- Adrenocorticotropin
 - (1) Adrenal cortices—hyperplasia
 - (2) Other glands—see 2 VI B 6 b (9)
- 3 Posterior lobe extracts
 - a Variable results depending on many factors especially the composition of the preparation²⁵
 - b Mucous membranes of stomach and lungs show areas of^{1 2 6 9 11 28 30}
 - (1) Hemorrhage
 - (2) Necrosis
 - (3) Ulceration
 - c Secretions of the following are decreased⁵
 - (1) Pancreas
 - (2) Stomach
 - (3) Saliva
 - d Galactagogue in certain species
 - e There is a decrease in
 - (1) Lymph flow
 - (2) Cerebrospinal fluid
 - f Cardiac hypertrophy (guinea pigs)³⁷
 - g Blood pressure—angiospasm of renal arteries and arterioles may produce pathologic lesions^{4 20}
 - h Intraocular pressure may fall¹³
 - i Renal influence on excretion of minerals is variable except for an increase in^{10 17}
 - (1) Sodium
 - (2) Chloride

- j Role in hypertension and toxemia of pregnancy is not known
- k Testicular growth may be depressed with injury to the tubular epithelium²²
- l Liver
 - (1) Fat may increase⁵
 - (2) Glycogen mobilization^{14 26}
- m Weight loss
- n Blood
 - (1) Red cells may increase in circulation^{6 7}
 - (2) Anemia may be severe^{4 7 11 18}
 - (3) Hematocrit may fall^{5 7}
 - (4) Volume may decrease
 - (5) Chemical analyses
 - (a) Decrease in
 - [1] Protein (total)
 - [2] Cholesterol (doubtful significance)^{19 21}
 - [3] Calcium (by intravenous administration)
 - [4] Fat (questionable)^{19 21}
 - (b) Increase in
 - [1] Potassium¹⁰
 - [2] Lactic acid but does not parallel blood sugar^{3 12}

E HISTOPATHOLOGY

- 1 The cellular origin of secretions (a summary of opinions)
 - a Introduction
 - (1) The following data are based on clinical and experimental evidence^{1 24 26 4 44}
 - (2) Pituitary hormones may be secreted in groups rather than singly¹⁵
 - b Anterior lobe
 - (1) Acidophilic cells may secrete the following hormones
 - (a) Growth (somatotrophic)^{28 29 40 4}
 - (b) Luteinizing (LH or prol. B)^{9-11 24 26 41}
 - (c) Lutetropic^{2 41}
 - (d) Lactogenic^{1 4 70 13 35}
 - (2) Basophilic cells may secrete the following hormones
 - (a) FSH (possibly from acidophils)^{1 4 6 11 70 7 3 34-38 45}
 - (b) TSH^{6 13 6 33}
 - (c) ACTH^{5 11 17 19 37 11}

- Intermediate lobe
 - (1) Secretions probably occur from its few cellular remnants
 - (2) Animals without this lobe may be dependent on other portions of pituitary gland
- d Posterior lobe
 - (1) Most likely forms its own principles but problem is unsettled
 - (2) Anterior or intermediate lobes may be original source of secretions
- 2 Pathway of secretions³⁰
 - a Anterior lobe—hormones pass directly into the blood stream
 - b Intermediate lobe—hormones may leave by the infundibular stalk (varies with species)
 - c Posterior lobe principles
 - (1) Enter cerebrospinal fluid of ventricle
 - (2) Diffuse through nervous tissue
 - (3) Act on parasympathetic center (tuber cinereum) in hypothalamus
- 3 Pituitary content of the different hormones (human)
 - a Gonadotropic hormones^{18 20 27}
 - (1) Fetus
 - (a) FSH—small amount
 - (b) LH—absent
 - (2) Children have small quantities
 - (3) Reproductive age—males have hypophyses with a potency 4 times that of females
 - (4) Old age
 - (a) Males—variable may have same values as castrates
 - (b) Females—high concentrations
 - (5) Castrates—large amounts
 - b Thyrotropic hormone (TSH)^{3 27 31}
 - (1) No alteration in concentration with
 - (a) Age
 - (b) Other factors i.e. pregnancy
 - (2) Average range of concentration within pituitary is 5 to 30 guinea pig units (see 2 VIII D 2)
 - c Lactogenic hormone—shows no change with⁷
 - (1) Age
 - (2) Sex
 - d Chromatophore (melanophore) stimulating hormone (?) content is unaltered by^{1 46}
 - (1) Age
 - (2) Sex
- F ACTIVITY AT DIFFERENT PERIODS IN LIFE
 - 1 Intrauterine
 - a Little is known concerning the role of fetal hormones in the presence of placental hormones
 - b It is possible that certain pituitary hormones may go through the placenta
 - 2 Infancy and childhood—all known hormones are active, except
 - a Gonadotropic
 - b Adrenocorticotrophic
 - (1) If it controls all factors of adrenal cortex, an uneven response occurs for
 - (a) Hair growth is limited
 - (b) Relative lymphocytosis is present
 - (c) Salt hormone effects may be normal
 - (d) 17 ketosteroids are low
 - (e) Urinary 11 oysteroids are same as adult
 - (2) Variation in above may be due to independent (or pituitary ACTH) level of adrenocortical activity
 - c Lactogenic
 - 3 Puberty
 - a Growth rate increases, probably due to a combined action of following hormones
 - (1) Growth
 - (2) Thyroid
 - (3) Adrenocortical
 - (4) Testosterone
 - (5) Female hormones indirectly
 - b Gonadotropic (FSH and LH) production increases with activation of basophilic cells
 - c ACTH may stimulate adrenal cortices to initiate sexual hair growth
 - 4 Menstruation
 - a Germ cell development is due to FSH causing
 - (1) Follicle formation
 - (2) Estrogen production
 - b At ovulation FSH increases

- c LH (see 57 VI B 1, 2 58 III A Chart 108 p 947)
 - (1) Secretion rises slowly, following menstruation until ovulation
 - (2) Corpus luteum stimulated for progesterone formation
 - d Luteotropic hormone maintains progesterone secretion
 - Vasopressin activity on uterine muscle at
 - (1) Ovulation (possibly)
 - (2) Menstruation
- 5 Maturity
- a All pituitary hormones except growth are at their maximum integration
 - b Gonadotropins vary with
 - (1) Menstrual cycles
 - (2) Pregnancy
 - c Gonadal hormones exert their pituitary control by
 - (1) Inhibition
 - (2) Stimulation
- 6 Pregnancy
- a FSH activity inhibited
 - b Cellular changes in pituitary (see 2 V D 2)
 - c Lactogenic hormone stimulated by withdrawal of placental hormones
 - d Oxytocic principle increases (rabbits)
- 7 Climacteric
- a Gonadotropic hypersecretion
 - (1) Males—rarely
 - (2) Females—fairly common
 - b Other hormones are still active, including perhaps small amounts of growth hormone
- 8 Old age
- a Gonadotropins
 - (1) Males—show a decline
 - (2) Females—persist or increase
 - b All remaining hormones probably decrease

VII CHEMISTRY

A ANTERIOR LOBE

- 1 Structure of hormones
 - a Exact chemical formulas are unknown
 - Protein molecules are the basic units of structure

- 2 Preparation (commercial)
 - a Variable methods exist for hormonal
 - (1) Extraction
 - (2) Purification
 - b Separation of pituitary hormones is accomplished by analysis of their chemical properties
- 3 Hormones which are now considered possible to isolate in chemically pure form or nearly so
 - a Growth^{1 2}
 - b Follicle-stimulating (thyliakentrin)^{3 4}
 - c Luteinizing (metakentrin)^{1 2 17 18 20}
 - d Thyrotropic^{1 2 10 31}
 - e Adrenocorticotrophic^{1 15 21 25 26}
 - f Lactogenic²¹
- 4 Chemical analysis
 - a Growth hormone (or pituitary glands)^{2 12 16}
 - (1) Molecular weight 47,300 ± 600
 - (2) Isoelectric point 6.85
 - (3) Contents which have been determined

	PER CENT
(a) Carbon	46.35
(b) Nitrogen	15.65
(c) Glutamic acid	13.40
(d) Hydrogen	7.07
(e) Tyrosine	4.3
(f) Methionine	3.06
(g) Cystine	2.25
(h) Sulfur	1.3
(i) Tryptophane	0.92
(j) Carbohydrate	■

 - (4) Properties
 - a Destroyed by
 - [1] Pepsin
 - [2] Trypsin
 - b More stable in alkali than acid medium
 - c Unstable at boiling water temperature
 - d Retained biologic activity in urea solutions
 - e In buffer of pH7
 - [1] Protein is coagulated at from 70° to 80°
 - [2] Growth potency is destroyed

- b Follicle stimulating hormone (sheep and hog pituitary glands)^{5 6 14}
- (1) Molecular weight 70,000
- (2) Isoelectric point (swine) 4.8
- (3) Contents (a glycoprotein)
- (a) Hog
- | | PER CENT |
|----------------|----------|
| [1] Mannose | 4.5 |
| [2] Hexosamine | 4.4 |
- (b) Sheep
- | | PER CENT |
|------------------|----------|
| [1] Carbohydrate | 10.13 |
| [2] Hexosamine | 8.0 |
- (4) Properties
- (a) Destroyed by
- [1] Ptyalin
- [2] Takadiastase
- [3] Amylase
- (b) Soluble in water
- (c) Relatively stable toward trypsin
- (d) Relatively heat stable
- c Luteinizing hormone (metakentrin, LH, ICSH)^{7 8 17 18 20 21}
- (1) Sheep pituitary glands
- (a) Molecular weight 40,000
- (b) Isoelectric point 4.6
- (c) Contents which have been determined
- | | PER CENT |
|------------------|----------|
| [1] Nitrogen | 14.2 |
| [2] Hexosamine | 5.8 |
| [3] Carbohydrate | 4.5 |
| [4] Mannose | 4.5 |
| [5] Tyrosine | 4.5 |
| [6] Tryptophane | 1.0 |
- (2) Swine pituitary glands
- (a) Molecular weight 100,000
- (b) Isoelectric point 7.45
- (c) Contents which have been determined
- | | PER CENT |
|------------------|----------|
| [1] Carbon | 49.37 |
| [2] Nitrogen | 14.93 |
| [3] Hydrogen | 6.83 |
| [4] Tryptophane | 3.8 |
| [5] Mannose | 2.8 |
| [6] Hexosamine | 2.2 |
| [7] Carbohydrate | 2.0 |
- (3) Properties common to both
- (a) Destroyed by proteolytic enzymes
- (b) Not destroyed by
- [1] Amylolytic enzymes
- [2] Ptyalin
- [3] Takadiastase
- (c) Inactivated by
- [1] Ketene
- [2] Cysteine
- d Thyrotropic hormone (sheep and beef pituitary glands) \approx 35
- (1) Molecular weight 10,000
- (2) Contents which have been determined
- | | PER CENT |
|---------------------------|------------|
| (a) Carbon | 45.6 |
| (b) Nitrogen | 12.6 or 13 |
| (c) Hydrogen | 6.09 |
| (d) Hexose | 3.5 |
| (e) Glucosamine | 2.5 |
| (f) Sulfur | 1.0 |
| (g) Phosphorus | 0 |
| (h) Carbohydrate grouping | |
- (3) Properties
- (a) Soluble in water and aqueous solutions of
- [1] Alcohol
- [2] Acetone
- [3] Pyridine
- (b) Insoluble in
- [1] Alcohol
- [2] Chloroform
- [3] Methanol
- [4] Hexachloroethane
- [5] Acetone
- [6] Ether
- [7] Pyridine
- (c) Precipitated from aqueous solution by the following acids
- [1] Phosphotungstic
- [2] Flavanic
- [3] Picric
- [4] Mercuric chloride
- (d) Not precipitated by dilute solutions of
- [1] Lead acetate
- [2] Sulfosalicylic acid (?)
- [3] Trichloroacetic acid (?)
- (e) Absorbed by
- [1] Protein precipitants
- [2] Colloidal ferric hydroxide
- [3] Benzoic acid
- [4] Animal charcoal
- [5] Permutit

- (f) Heat labile in oxygen (absence or presence)
- (g) Inactivated by
- [1] Cysteine
 - [2] Ketene
 - [3] Benzoyl chloride
 - [4] Nitrous acid
 - [5] Trypsin
 - [6] Pepsin
- (h) Protein color reactions
- e Adrenocorticotrophic hormone (sheep and swine pituitary glands)^{5 10}
- (1) Molecular weight 20 000
 - (2) Isoelectric point 4.7
 - (3) Content
- | | PER CENT |
|------------------|-------------|
| (a) Carbon | 46.35 50.64 |
| (b) Nitrogen | 15.65 15.47 |
| (c) Cystine | 7.19 |
| (d) Hydrogen | 5.89 6.23 |
| (e) Sulfur | 2.30- 2.33 |
| (f) Methionine | 1.93 |
| (g) Carbohydrate | 0 |
| (h) Phosphorus | 0 |
- (4) Properties
- (a) Soluble in water
 - (b) Stable at 100° C unlike all other pituitary hormones
 - (c) Stable toward pepsin
 - (d) Inactivated by trypsin
- (5) Essential groups for biologic action
- (a) Amino
 - (b) Phenolic hydroxyl
- f Lactogenic hormone (sheep and ox pituitary glands)^{11 12 22 24}
- (1) Molecular weight 25 000 to 32 000
 - (2) Isoelectric point 5.73
 - (3) Content
- | | PER CENT |
|-------------------|----------|
| (a) Carbon | 51.81 |
| (b) Nitrogen | 16.5 |
| (c) Glutamic acid | 12.3 |
| (d) Arginine | 8.3 |
| (e) Hydrogen | 6.81 |
| (f) Tyrosine | 4.5 5.7 |
| (g) Methionine | 4.3 |
| (h) Cystine | 3.0-3.4 |
| (i) Tryptophan | 1.2 2.5 |
| (j) Sulfur | 1.8 2.0 |
| (k) Phosphorus | 0 |

- (4) Properties
- (a) Destroyed by
 - [1] Pepsin
 - [2] Trypsin
 - (b) Soluble in absolute methyl or ethyl alcohol
 - (c) Insoluble in water
 - (d) Thermolabile (altered by various factors)
 - (e) Inactivated by
 - [1] Mild hydrolysis
 - [2] Reagents affecting amino acids or disulfide groups
 - [3] Iodine
 - (f) Treatment with urea increased the viscosity of solutions with loss of potency

B INTERMEDIATE LOBE²

- 1 Specific metabolic factor (?)
- a Formula is unknown
 - b Properties
 - (1) Destroyed by prolonged treatment with trypsin
 - (2) Resistant to
 - (a) Alkalies
 - (b) Peptic digestion
 - (c) Heat
 - (3) Thermostable in aqueous solution
- 2 Melanophore stimulating factor (?)
- a Formula not determined
 - b Constituents that are known
 - (1) Tyrosine
 - (2) Arginine
 - (3) Cystine
 - c Properties
 - (1) Destroyed by prolonged boiling with mineral acids
 - (2) Stable to
 - (a) Boiling alkalis (therefore not identical with vasopressin or oxytocin)
 - (b) Dilute acetic acid
- C POSTERIOR LOBE²⁸⁻³⁰
- 1 Mother molecule
 - a Ratio of three hormones 1:1:1
 - b Molecular weight 30,000
 - c Isoelectric point 4.8
 - d Contents which have been determined
 - (1) Exact formula is unknown for any of the principles

(2) Amino acids which are present

- (a) Cystine
- (b) Tyrosine
- (c) Arginine

PER CENT

- (3) Carbon 48.64
- (4) Nitrogen 15.00
- (5) Oxygen 22.89
- (6) Hydrogen 6.63
- (7) Sulfur 3.00

■ Properties—activity destroyed by

- (1) Dilute acids
- (2) Alkalis
- (3) Enzymes of gastro intestinal tract

VIII BIO ASSAY

A INTRODUCTION

- 1 Unknown preparation of the hormone
 - injected into different types of animals under special conditions
- 2 Many of the tests are difficult to perform
- 3 Results are variable

B GROWTH HORMONE

- 1 Methods (rats usually employed)
 - a Hypophysectomized (male or female) animals are used to determine
 - (1) Resumption of body growth^{1, 2}
 - (2) Weight gain^{1, 2}
 - (3) Increase in tail length^{3, 4}
 - (4) Change in width of uncalcified cartilage at proximal epiphysis of tibia^{4, 9, 14}
 - b Resumption of body growth in normal plateaued females⁵
 - Other less frequent experiments by finding
 - (1) Decrease in the following¹¹
 - (a) Glutathione content of liver¹⁰
 - (b) Nitrogen excretion
 - (c) Urea (blood and tissues)
 - (d) Amino acids of
 - [1] Blood
 - [2] Tissues
 - (e) Nonprotein nitrogen
 - (2) Increase in size of liver

2 Units

- a Normal, plateaued rat—the amount of any preparation that will produce a gain of 40 Gm in total body weight with 17 injections by 20 days

25

- b Hypophysectomized rat—the amount of any preparation that will produce a gain of 10 Gm in total body weight with 9 injections by 10 days

C GONADOTROPINS

- 1 Follicle stimulating hormone (substance must be free of luteinizing hormone)

a Methods

- (1) Weight gain in
 - (a) Ovaries (hypophysectomized or immature rats)^{1, 4, 5}
 - (b) Uterus (normal mice)⁸
 - (c) Testes (hypophysectomized rats)⁴
- (2) Estrus vaginal smears¹¹
- (3) Histologic examination for beginning follicular development (hypophysectomized rats)^{6, 7}

b Units

- (1) Rat—minimal amount of unknown given subcutaneously one third the total amount injected daily over a 3 day period into hypophysectomized female rats (26 to 28 days old at operation and 6 to 8 days postoperatively) which causes resumption of follicular growth within 72 hrs after the last dose⁷
- (2) Mouse—the smallest amount of preparation which, given subcutaneously to 5 or more mice (21 to 23 days old) in one third portions at 24 hr intervals, produces from 100 to 150 per cent increase in uterine weight by 72 hrs⁸
- 2 Luteinizing hormone (or interstitial cell stimulating hormone)
 - a Methods
 - (1) Weight gain in
 - (a) Ovaries (normal, immature hypophysectomized rats)^{1, 4}
 - (b) Seminal vesicle (normal immature rats)^{1, 4}
 - (c) Testes (normal immature pigeons or 1 day old chicks)¹⁰
 - (d) Ventral lobe of the prostate (hypophysectomized male rats)⁴

- (2) Repair in ovarian interstitial tissue (hypophysectomized rats) ^{5 8}
- (3) Melanin reaction in feathers of African weaver finches¹¹

b Units

- (1) Ovarian weight—minimal amount given intraperitoneally one third the amount injected daily for 3 days, into hypophysectomized rats (26 to 28 days old at operation and 6 to 8 days postoperatively) which will cause repair of deficient interstitial cell tissue of ovary with in 72 hrs after the last dose^{1 4}
- (2) Ventral prostate weight—the amount given subcutaneously is 1 cc (representing $\frac{1}{4}$ of total dose) once daily for 4 days into hypophysectomized immature male rats (21 to 22 days of age at operation the injections start 2 days postoperatively) the autopsy is performed on the fifth day and the increase in weight of the ventral prostate is determined⁴

D THYROTROPIC HORMONE

1 Methods—thyroid gland has been used as an index of potency

a The changes are determined by

- (1) Weight—increased^{1-9 10 11 14 20}
_{22 23 5}
- (2) Iodine content—decreased^{10 16 27}
- (3) Cytologic alterations^{1 11 12, 13}
_{15 16 19 25 26 28}
- (4) Combinations of (1) and (3)

b The following normal immature animals are used

- (1) Guinea pigs^{9 10 13 19 12 20 23 7}
- (2) Chicks (1 to 3 days old)^{6 7 9 11}
_{21 23 27}
- (3) Rats (may be hypophysectomized)^{8 10 1}
- (4) Tadpoles (axolotls)^{10 4}

2 Units (each varies with the type of test)

- a International standard—1 unit is equivalent to 250 micrograms of the preparation²¹

b Guinea pig

(1) Junkmann Schoeller¹⁵

- (a) One—the least amount given daily which produces unmistakable alterations in the thyroid cells over a 4 day period, i.e., beginning cuboid to cylindrical epithelium and diminishing colloid in 2 infantile guinea pigs (100 to 150 Gm)
- (b) Two—daily requirement that results in well marked changes beyond the border line
- (c) Three—daily quantity that produces practically no colloid and the follicles have very small lumens

(2) Rowland Parkes—the total amount injected daily for 5 days into a 200 Gm female guinea pig which will cause the thyroid to double its weight or attain a weight of 60 mg²⁰(3) Bergmann Turner—the total amount of hormone injected subcutaneously for 5 days which will produce a 50 per cent mean weight increase in the thyroids of 10 male animals (average weight 115 ± 15 Gm)⁶c Chick⁶

- (1) Total amount of hormone injected subcutaneously daily over a 4 day period which will cause a mean increase in weight of 20 per cent (or 50% in males) in the thyroids of 20 chicks (average weight of 55 ± 10 Gm)
- (2) This unit is about one fourth of the guinea pig unit

E ADRENOCORTICOTROPIC HORMONE

1 Methods

a Adrenal gland weight increase determined in

(1) Rats^{7 8 1}

(a) Normal 4 or 21 days old

(b) Hypophysectomized (maintenance test)^{1 12 13}(c) Hypophysectomized and unilateral adrenalectomy^{4 18 12}

(2) Chicks 2 days old

- b Redistribution of cortical lipids in adrenals of hypophysectomized, mature female rats (repair test)^{6 13}

- c Cholesterol or ascorbic acid content in adrenals of

(1) Rats

- (a) Normal immature (24 days old)¹⁰

- (b) Hypophysectomized — one adrenal removed and its ascorbic acid content compared with remaining one after intravenous injections of hormonal preparation¹¹

- (2) Guinea pigs (300 to 450 Gm)¹¹

- d Determination of mitoses in the cells of adrenal cortex of guinea pigs³

2 Units

- a Repair—total dose in milligrams necessary to start redistribution of lipids and an increase in width of the adrenal cortical in female rats, 26 to 28 days old at time of hypophysectomy and 14 days postoperatively, given 4 daily intraperitoneal injections¹³

- b Maintenance—daily dose in milligrams required to maintain proper adrenal weight for 15 days in hypophysectomized male rat at 40 days of age⁶

- c Sudanophobic—the smallest amount of substance which is injected twice daily for 8 days into hypophysectomized rats (weighing from 80 to 120 Gm from 10 to 20 days postoperatively after one adrenal is removed and stained with Sudan and examined for development of the Sudanophobic zone) which will restore the Sudanophobic zone to normal (compared with previously removed adrenal)⁹

- d Ascorbic acid—the substance is injected intraperitoneally thrice daily for 3 days (4 mg/100 Gm of body weight) into 24 day old rats or guinea pigs (300 to 450 Gm), then the ascorbic acid content of the adrenals is determined and compared with a standard¹⁰

F LACTOGENIC HORMONE

- 1 Riddle Bates, (preferred method)^{1 4 6 12}

a Method

- (1) Minimal amounts of unknown are injected intramuscularly in to pigeons

- (2) Weight of excised crop gland is determined

- b Unit—the smallest concentration of substance given intramuscularly daily for 4 days into 2 to 3 month old pigeons which will cause within 96 hrs after the first injections an increase in the weight of their crop glands

2 Lyons³

a Method

- (1) Crop glands of pigeons are injected intradermally for 4 days with the unknown extract

- (2) Pigeons are killed on the fifth day

- (3) Sacs are dissected and examined against the light with naked eye

- b Unit—the amount required for a majority of 5 injected birds to show positive crop responses

3 Reece Turner¹¹

a Method

- (1) Unknown preparation is injected intradermally over the crop gland area of pigeons

- (2) Degree of response is determined

- b Unit—the amount of hormone which when injected intradermally over the crop gland for 4 days, will cause an area of proliferation there about the size of a nickel

4 Minimum micro unit (Missouri)

a Method

- (1) Intradermal injections of unknown are given over the crop sac

- (2) Glands are examined and rated by viewing them by transmitted light

- b Unit—the amount of hormone injected intradermally over the crop gland of 20 common pigeons which will elicit a minimal response in 50 \pm 11 per cent of the pigeons

5 McShan Turner¹⁰

a Method—breast muscles of pigeons are injected with unknown material

■ Unit—the amount of hormone injected during 4 days which will cause a minimum proliferation of crop glands of 50 ± 11 per cent of 20 common pigeons

6 Gardner Turner (rabbit unit)³

a Method

(1) Pseudopregnancy ■ induced in rabbits by an intravenous injection of chorionic gonadotropic substances (50 rat units)

(2) On fourteenth day, mammary glands are checked for development

(3) For next 6 days lactogenic preparation ■ injected

(4) On seventh day, the degree of enlargement and the secretion of mammary glands are rated

(5) Rating—mere duct lactation (one plus) to lactation observed in parturient animals (four plus)

b Unit—the response to an average plus three rating showing that entire gland is filled with milk in at least 6 animals (definite rating basis is established)

7 Guinea pig (nulliparous) may be used by determining lactation response^{4, 7}8 International unit³

a Method

(1) Administration of unknown by either local or systemic route

(2) Crop gland growth determined in pigeons and doves

b Unit—1 unit is the amount of activity contained within ■ 1 mg (100 gamma) of standard preparation

■ Relationship of units

	Units/Gm of initial extract*	Relation to McShan Turner unit
a Riddle Bates	3 750	1 5
b Lyons macro units	1 875	0 75
c Reece Turner	55 556	22 2
■ Minimum micro method	444 445	177 8

	Units/Gm of initial extract*	Relation to McShan Turner unit
e McShan Turner	2,500	1 0
f Gardner Turner	9 2	0 0037

* Purified hormone was not used

G MAMMOGEN I (?)¹

1 Method—development of mammary ducts in male albino mice (normal rudimentary glands do not respond to gonadotropic hormones)

2 Unit—total amount of tissue or extract, given subcutaneously once daily for 6 days, which produces definite signs of duct development in one or more glands of 50 ± 10 per cent of 10 male albino mice weighing 10 to 25 Gm the glands are removed and analyzed on the seventh day

H MAMMOGEN II (?)¹

1 Method

a Lobule alveolar development of mammary glands in ovariectomized, virgin mice

b Results compared with glands from mice that are from 4 to 8 days pregnant

2 Unit—the amount required per mouse, injected subcutaneously for 10 days, to obtain definite lobule alveolar development in 50 ± 10 per cent or more castrate nulliparous female mice (weight 12 to 18 Gm)

I FAT METABOLISM HORMONE (?)^{1,3}

1 Methods

a Guinea pig (female)—depression of fat plasma is determined after injection of pituitary extract

b Rabbit—reduction of fat (blood) around 36 per cent in 6 to 8 hrs with a single injection of anterior pituitary extract³

c Mouse—fatty infiltration of liver

2 Unit—minimum amount of extract which will depress plasma fat of at least 6 guinea pigs on the average of 30 to 50 per cent of the normal (60 mg %)

J SPECIFIC METABOLIC PRINCIPLE¹

1 Method

- a A definite amount of preparation is given subcutaneously to the animal
- b Certain precautions are necessary in preparing the material (vasopressin, thyrotropic hormone, dosage, and so forth must be considered)
- c The following animals may be used
 - (1) Rabbits (most sensitive)
 - (2) Rats
 - (3) Guinea pigs
- d Respiratory quotient decreases at a definite interval following the injection

2 Unit (rabbit)

- a The minimal amount given subcutaneously to a 2 kg rabbit which will cause the maximal metabolic stimulation around the third hour
- b One cc produced a
 - (1) Twenty per cent increase of metabolism
 - (2) Reduction of 0.12 in respiratory quotient

K MELANOPHORE STIMULATING FACTOR

1 Frogs (hypophysectomized)

a Methods

- (1) Activity is determined by the time required for the melanophores to return to full contraction after injection of the preparation^{1 6 8 12 13}
 - (a) Comparison of an unknown with a known amount of hormones
 - (b) Difficult test
- (2) Perfusion of frog's legs^{1 7 13}
 - (a) Frog is pithed
 - (b) Ringer's solution is used until melanophores are contracted
 - (c) A given amount of unknown extract is added to the solution after two of the frog's legs are tied off as controls
 - (d) Perfusion
 - (e) The color change is determined within a definite time
 - (f) The threshold of concentration is found for the solution by several trials
 - (g) Difficult test

(3) Perfusion of frog's skin [based on methods (1) and (2)]⁹

b Unit—not defined

2 Toads (hypophysectomized)¹¹

a Method

- (1) Same as for frogs [method 1]
- (2) Modified test

- (a) Extract is injected into dorsal lymph sac of toad which is fully pale (animal is kept on white background in order to lose its pigment)
- (b) About 10 per cent accuracy, results are not influenced by other posterior lobe principles

b Unit (international)—melanophore activity is that amount in 0.5 mg of international standard posterior lobe powder

3 Fish

a Minnow (*Phoxinus phoxinus*)

(1) Method

- (a) The amount of hormone producing a red area (erythrophore response) of 4 to 9 sq mm at the attachment of the fin is determined^{14 15}
- (b) Animal cannot be used during breeding season
- (c) Nonspecific test
- (d) Modification of procedure degree of response in an isolated fin or scales immersed in solution may be measured microscopically^{3 5}

(2) Unit—this is based on the size of the red color reaction

b Atlantic minnow (*Fundulus heteroclitus*)

- (1) Method—melanophore expansion at the denervated caudal area test is rapid and accurate
- (2) Unit—the amount of hormone producing a darkening of the denervated caudal area in 25 per cent of minnows within 30 min after intraperitoneal injection

4 Lizard (*Anolis*)¹⁰

a Method

- (1) Hypophysectomized animal is injected intraperitoneally with solution

(2) Degree of pigment dispersion is determined

(3) Color changes fall into a definite stage, which is given a numerical value

(4) Better test than others

b Unit—weight of pituitary powder which, injected into these animals after being in the form of neutralized sodium hydroxide extract produces a color response

L VASOPRESSIN

1 Methods

a Blood pressure in decerebrate animals^{4 7}

b Solution to be assayed is injected into vein of anesthetized dog or cat^{1 6}

(1) Blood pressure increase is compared with a known standard

(2) Most commonly used test

c Smooth muscle (ileum) contractions of guinea pig are evaluated⁸

2 Unit

a One unit represents the activity that is exhibited by 0.5 mg of U S P standard powdered pituitary (based on pressor activity) in anesthetized dog or cat)

b One milligram of international standard powder represents about 7 mg of fresh posterior lobe (ov)

M OXYTOCIN

1 Methods

a Guinea pig (immature) (official method)

(1) Muscular response of isolated uterus immersed in modified Locke's solution is compared with a standard preparation^{1 2}

(2) Other animals may be used

(a) Sheep (less sensitive)^{6 7}

(b) Puerperal cat⁷

(c) Rabbit¹³

b Chickens or roosters—by study of blood pressure effects⁸⁻¹¹

2 Unit

a One unit represents the activity of 0.5 mg of standard powder (U S P)

b Preparation is adjusted to an activity of 10 units/cc of solution

N ANTIDIURETIC FACTOR

1 Methods

a Water diuresis inhibition^{2 3 8}

(1) Unanesthetized animal (rats, mice)

(a) The amount of extract required to delay the excretion of administered water is determined

(b) Water is given by either stomach tube or intraperitoneal injections

(c) Animals are hydrated by 5 per cent of body weight of water^{4 9 10}

(d) A curve is plotted of the urine elimination at definite intervals determined by the maximum time of output and also the time required for excretion of half the administered water^{2 3}

(e) Findings are compared with the controls for calculation of results^{9 11 12}

(f) Anti diuretic effect is inversely proportional to the water load

(g) Preferred test

(2) Dogs with bladder fistulas may be used¹⁰

(3) Animals (rats rabbits) are rendered diuretic by water or alcohol, and the minute anti diuretic action of pitressin can be detected^{7 13}

b Changes in body water (frogs)¹

c Chloruretic effect of posterior lobe preparations (rats)

d Diabetes insipidus (dogs female)⁶

(1) Unknown material given intravenously

(2) Ratio of urinary creatinine plasma creatinine determined

(3) Response is compared with standards

(4) Amounts of antidiuretic material is detected readily in

(a) Tissue

(b) Blood

(c) Urine

2 Unit—not well defined

IX PATHOLOGY

A GROSS

TABLE 6 SURGICAL PATHOLOGY OF COMMON
TUMORS IN OR ADJACENT TO SELLA
TURCICA (HORRAX⁴⁰)

	SIZE	APPEARANCE	CAPSULE	LOCATION	POSSIBLE EXTENSIONS
Chromophil	From almost microscopic to large*	Rounded smooth reddish gray†	Thin few small blood vessels on surface	Intrasellar central or may be largely unilateral	May push through diaphragm displacing one or both optic nerves upward or to sides bury deep into sphenoid sinus or extend in frontal lobe and third ventricle
Chromophobe	1 cm in diameter to large	Rounded smooth reddish gray	Thin few small blood vessels on surface‡	Intrasellar	May push through diaphragm displacing one or both optic nerves upward or to sides bury deep into sphenoid sinus or extend to frontal lobe and third ventricle Greater tendency to displace both optic nerves than in chromophil
Cranio pharyngioma	2 to 3 cm to very large	Pale or yellowish translucent bulging	Thin or very dense and thick	Usually above sella but may be intrasellar	May extend in any direction occasionally back as far as pons may surround sella
Meningioma	2 to 3 cm to very large	Granular grayish red	Resistant and thin	Above and attached to tuberculum sellae	Usually localized above site of origin
Glioma	1 cm to very large	Grayish white	Little or none present	In one or both optic nerves or chiasm	Forward to one or both orbits or back to chiasm
Epidermoid	2 to 3 cm to very large	Mother of pearl	Fine (one layer of epithelium)	Midline under optic nerves	May extend back along base of skull
Aneurysm of internal carotid	1 cm to large	Smooth color as that of large artery may not pulsate	Fibrous covering as in all blood vessels	Adjacent to sella	Expands against sella

* Large can be considered size of hen's egg

† The reddish gray color approaches that of a large artery

‡ When degenerated and/or cystic appearance changes

B MICROSCOPIC INCLUDING HISTOPHYSIOLOGY

1 Introduction

- A great variety of lesions have been found in the hypophysis
- The following summary does not attempt to correlate the pathology with clinical states
- Animal experiments included here may demonstrate similar effects in humans

2 Atrophy⁴¹

- Variable changes
- Eosinophils—absent
- Lymphocytes—present
- Fibrosis
- Hyaline degeneration
- Causes
 - (1) Arteriosclerosis
 - (2) Embolus
 - (3) Inanition
 - (4) Trauma

- 3 Pressure atrophy⁴⁴
 - a Cells shriveled, may not be recognized
 - b Colloid—scarce
 - Fat deposits
 - d Edema due to hydrocephalus
- 4 Hypoplasia
 - a Pituitary size—decreased
 - b Chromophobes (small) —predominant
 - Eosinophils—few, if any (dwarfism)⁴⁶
 - d Causes same as for atrophy (see above)
- 5 Regeneration of tissue may occur following postpartum necrosis (Sheehan's disease)⁴¹
- 6 Necrosis⁴¹ ■
 - a Characteristic findings for any necrotic tissue
 - b Causes
 - (1) Embolus
 - (2) Thrombosis
 - (3) Infection
 - (4) Tuberculosis
 - (5) Syphilis
 - (6) Tumor
 - (7) Eclampsia
 - (8) Miscellaneous
- 7 Other degenerative changes
 - a Types
 - (1) Hyaline
 - (2) Amyloid
 - (3) Hemosiderin (hemochromatosis)
 - (4) Lipoid
 - (5) Calcium
 - (6) Cholesterol deposits
 - (7) Colloid accumulations within follicularlike structures
 - (8) Hydropic
 - (9) Fatty
 - b Causes are as listed under II 2 to 6 above
- 8 Congestive hyperemia⁴⁴
 - a Blood vessels often are
 - (1) Enlarged
 - (2) Increased in number
 - b Causes
 - (1) Congenital heart anomalies
 - (2) Congestive heart failure
 - (3) Polycythemia
 - (4) Emphysema
- 9 Hemorrhage⁴⁴
 - a Extravasation of blood into surrounding tissues
 - b Causes
 - (1) Skull fracture
 - (2) Necrosis
 - (3) Sepsis
 - (4) Miscellaneous
- 10 Infarct⁴¹ ■
 - a Large or small ones may be found
 - b Causes
 - (1) Endarteritis which may be
 - (a) Embolic
 - (b) Bacteremic
 - (c) Thrombotic
 - (d) Arteriosclerotic
 - (2) Postpartum hemorrhage, if sufficiently severe produces an 'anemic infarct'
- 11 Specific diseases (rare)⁴⁴
 - a Syphilis
 - b Tuberculosis⁴⁴
 - c Anthrax
 - d Leukemia
- 12 Tumors
 - a Chromophobes⁴¹
 - (1) Embryonic type of cell common
 - (2) Acidophils—rarely
 - (3) Cytoplasm—pale often vacuolated
 - (4) Nuclei—not much larger than endothelial cell nuclei
 - (5) Granules—absent
 - (6) Nuclei
 - (a) Round
 - (b) Irregular
 - (7) Alveolar arrangement of cells may occur
 - (8) Colloid is present in
 - (a) Cells
 - (b) Alveoli
 - (9) Connective tissue variable
 - (10) Tumor may be
 - (a) Solid, tough, like muscle
 - (b) Cystic occasionally
 - b Acidophils⁴¹
 - (1) Cells—arranged in strands and alveolarlike structure
 - (2) Cytoplasm—eosinophilic
 - (3) Nuclei
 - (a) Ovoid or round
 - (b) Sharply stained
 - (c) Two times larger than endothelial cell

- (4) Malignant type of tumor does not retain alveolarlike arrangement (see Fig 23)
- (5) Adenoma structure may not be present, but rather a diffuse or nodular hyperplasia
- Basophilic—see 11 \ B 1
- d Mixed
 - (1) Cells may be combination of
 - (a) Acidophils
 - (b) Chromophobes
 - (c) Nondescript type
 - (2) Little resemblance to normal arrangement
 - (3) Groups of irregular masses with sharp boundaries
- Craniopharyngioma^{18 81}
 - (1) It is called
 - (a) Craniopharyngeal duct tumor
 - (b) Rathke's pouch tumor
 - (c) Suprasellar cyst
 - (d) Adamantinoma
 - (2) Solid
 - (a) Epithelial nests are
 - [1] Made of multiple projections
 - [2] Lined by cylindrical cells arranged in concentric circles
 - [3] Surrounded by loose connective tissue
 - (b) Various changes may develop
 - [1] Necrosis
 - [2] Small horny bodies
 - [3] Tiny pseudocystic areas
 - [4] Calcification
 - [5] True bone tissue from sclerotic hyaline fibrosis and may be mistaken for teratoma
 - [6] Malignant degeneration occasionally (prickly and smooth cells)
 - (3) Cystic—true type may be lined with
 - (a) Fibrous tissue
 - (b) Papillary outgrowths in which degenerative changes take place
- f Miscellaneous
 - (1) Sarcoma
 - (2) Lymphosarcoma
 - (3) Fibroma
 - (4) Angioma
 - (5) Teratoma
 - (6) Psammoma
 - (7) Lipoma
 - (8) Cholesteatoma (from cranio-pharyngioma or epidermoid carcinoma)
 - (9) Carcinoma^{8 10 20}
 - (10) Metastatic lesions from
 - (a) Brain
 - (b) Breast
 - (c) Bronchus
 - (d) Prostate
 - (11) Cysticercus
 - (12) Echinococcus
- 13 Hyperplasia (general) has been noted in
 - a Gigantism
 - b Acromegaly
 - c Myxedema (see below)
 - d Hyperthyroidism (see below)
 - e Castration (physiologic or surgical)
 - f Pregnancy
 - g Hypertension (?)
- 14 Myxedema or thyroidectomy^{1 70 80-8 90 93 99 100}
 - a Acidophils
 - (1) Greater decrease than in castration
 - (2) Colloid content increased^{1 10}
 - b Basophils—increased
 - (1) Findings similar to those with castration, but may be differentiated by special staining methods
 - (2) Vacuolization is usually found
 - c Pituitary size—increased^{1 6 31 3 43 51 55 64 68 73 74}
 - d Changes are almost identical with those of thyroidectomized animals^{1 70}
- 15 Hyperthyroidism^{50 70 8}
 - a No specific change in normal pituitary cytology has been established
 - b Acidophils
 - (1) Numbers—decrease but do not disappear
 - (2) Granules—brilliant
 - (3) Golgi apparatus—hypertrophied
 - (4) Mitochondria—enlarge

- c Basophils increase in
 - (1) Size
 - (2) Number
 - (3) Vacuolization
- d Pituitary may decrease in size^{19 26}
- 16 Addison's disease^{2 1, 3 4 47 50 57}
 - a Acidophils—decreased
 - b Basophils—decreased (anterior and posterior lobes)
 - c Chromophobes—increased
- 17 Hyperadrenocorticalism—findings similar to basophilism (see 11 \ B 1)
- 18 Pancreatectomy—basophils are²⁷
 - a Enlarged markedly
 - b Degranulated
 - c Vacuolated
 - d Similar to hyalinized Crooke cells (see 11 \ B 1)
- 19 Hypertension^{1 13 15 16 18 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100}
 - a Clinical entities in which basophilic changes may be significant are
 - (1) Eclampsia
 - (2) Nephritis
 - (3) Nephrosclerosis (benign or malignant)
 - (4) Essential type
 - b Basophils increase in
 - (1) Posterior lobe with hypertension
 - (2) Anterior lobe with diseases of the kidneys
 - c Significance of the pituitary cytology found in these conditions is still unsettled
- 20 Chorionepithelioma and teratoma^{1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100}
 - a Acidophils—decreased
 - b Changes similar to those of pregnancy
- 21 Carcinoma of breast—no significant changes¹¹³
- 22 Effects due to administration of different preparations (Ordinary laboratory animals were used results have been controversial due to many variable factors i.e dosage age type of animal and so forth)
 - a Growth hormone⁴
 - (1) Chromophobes—increase
 - (2) Acidophils—decrease
 - (3) Basophils—no change
 - (4) Pituitary size—normal
 - b Adrenocorticotrophic hormone⁴¹
 - (1) Basophils—increase in size
 - (2) Pituitary weight—decreased
 - c Parathyroid hormone—acidophils are decreased (opposite with parathyroidectomy)⁴
 - d Male sex hormone (testes extracts or androgenic preparations)
 - (1) Cytologic effects are similar to administered estrogens^{11 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100}
 - (2) Pituitary weight is not altered in normal or spayed rats^{43 50-53}
 - e Estrogens^{10 11 23 24 25 103}
 - (1) Chromophobes
 - (a) Number—increased¹⁰¹
 - (b) Mitotic activity—remains unchanged
 - (2) Acidophils
 - (a) Number—decreased¹⁰¹
 - (b) Mitotic activity—enhanced
 - (c) Golgi apparatus—hyper trophied
 - (d) Hyperplasia⁹⁵
 - (3) Basophils
 - (a) Number—decreased
 - (b) Mitotic activity—unaffected
 - (c) Golgi apparatus—very large
 - (d) Mitochondria—numerous
 - (e) Degranulation occurs^{21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100}
 - (4) Other demonstrated changes
 - (a) Pituitary gland shows great hypertrophy and weight increase^{2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100}
 - (b) Eosinophilic hyperplasia produced in humans by prolonged and large doses of estradiol¹⁰¹
 - (c) Reversion to normal pituitary cytology following ovariectomy^{11 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100}
 - f Progesterone
 - (1) Pituitary weight may increase⁷⁷
 - (2) Castration effects found in pituitary remain the same³⁷
 - g Castrate urine, placental or fetal extracts change chromophobe cells
 - (1) Number—increased
 - (2) Degranulation
 - h Insulin injections (repeated)-⁴
 - (1) Results—inconsistent
 - (2) Acidophils—involved probably

- i Thymus extract—acidophils are increased (?)⁴
- j Antigonadotropins⁸³
 - (1) Chromophobes are rarely found in typical areas
 - (2) Acidophilic stain modified
 - (3) Basophils show
 - (a) Hyalinization
 - (b) Vacuolation
 - (c) Replacement by large, sparsely granulated cells, rich in mitochondria
 - (4) Pituitary
 - (a) Hyperemic
 - (b) Edematous
- k Goitrogenic agents produce same effects as with thyroidectomy⁸
 - (1) Sulfaguanidine⁵
 - (2) Thiouracil⁷²
 - (3) Promizole³⁶
- l Vitamins
 - (1) A and C (rabbits)³
 - (a) Acidophils—increased
 - (b) Basophils—increased slightly
 - (2) B deficiency (humans)¹
 - (a) Pars glandularis may have necrotic areas
 - (b) Adenomalike arrangements of oxyphils and basophils
 - (3) E deficiency—castration changes may be found (rats)⁶⁰
 - (4) D—oxyphils affected (dogs)⁶⁵

X CLASSIFICATIONS

A COMPREHENSIVE LIST OF CHIEF FACTORS IN ENDOCRINE DISEASES

- 1 Etiologic
 - a Congenital
 - b Hereditary
 - c Nutritional (including vitamins)
 - d Chemical
 - e Infection
 - f Radiation
 - g Surgical
 - h Hormonal
 - i Malignancy
 - j Neuropsychic (via hypothalamus)
 - k Unknown
 - l All others
- 2 Gross anatomic and pathologic
 - m Normal
 - b Atrophic

- c Absent
 - d Hypertrophy
 - e Hyperplasia
 - f Abnormal location by extension
 - g Aberrant
 - h Adenomatous
 - i Cyst
 - j Aneurysm
 - k Malignant
 - (1) Primary
 - (2) Secondary
 - l Acute inflammation
 - (1) Suppurative
 - (2) Nonsuppurative
 - m Chronic inflammation
 - (1) Suppurative
 - (2) Nonsuppurative
 - n Hemorrhage
 - o Infarct
 - p Thrombosis
 - q Necrosis
 - r Other degenerative changes
 - s Compression
 - t Metastases
 - u Postoperative remnants
 - v Recurrent
 - w Calcification
- 3 Hormonal
 - m Present
 - (1) Normal
 - (2) Normal without end organ response
 - (3) Hyposecretion
 - (4) Hypersecretion
 - (5) Premature
 - b Past
 - (1) Normal
 - (2) Normal without end organ response
 - (3) Hyposecretion
 - (4) Hypersecretion
 - (5) Premature
 - 4 Histologic
 - a Normal
 - b Hypoplasia
 - m Atrophy
 - d Hypertrophy
 - e Hyperplasia
 - f Adenomatous
 - g Hemorrhage
 - h Infarct
 - i Suppurative
 - j Nonsuppurative

- k. Carcinoma
 - l. Degenerative and infiltrative changes
 - (1) Hyaline
 - (2) Fatty
 - (3) Fibrotic
 - (4) Pigmentary
 - (5) Lymphocytic
 - (6) Leukemic
 - (7) Malignant
 - (8) Hydropic
 - (9) Others
 - m. Regeneration
 5. Therapeutic
 - a. Present
 - (1) None
 - (2) Surgical
 - (3) Radiation
 - (4) Drugs
 - (5) Hormonal
 - (6) Dietary
 - b. Past
 - (1) None
 - (2) Surgical
 - (3) Radiation
 - (4) Drugs
 - (5) Hormonal
 - (6) Dietary
- B. HORMONAL**
1. Hyposecretion
 - a. Growth hormone
 - (1) Prepuberal
 - (a) Pituitary dwarfism
 - (b) Cretinism (see 24 XI)
 - (2) Midpuberal i.e., puberal arrest
 - b. Gonadotropic hormones
 - (1) Follicle-stimulating and luteinizing hormones
 - (a) All panhypopituitary cases
 - (b) Selective "FSH" deficiency (eunuchoidism or secondary amenorrhea)
 - (2) Follicle stimulating hormone—no clinical syndrome known
 - (3) Luteinizing hormone
 - (a) Pubescent males with follicle stimulating hormone which is normal or increased
 - (b) Failure of ovulation
 - (c) Menstruation
 - [1] Normal
 - [2] Amenorrhea
 - [3] Excessive bleeding
 2. Hypersecretion
 - a. Growth hormone
 - (1) Prepuberal—gigantism
 - (2) Midpuberal — acromegalic gigantism
 - (3) Postpuberal—acromegaly
 - b. Gonadotropic hormones
 - (1) Follicle stimulating and luteinizing hormones
 - (a) Acromegaly possibly
 - (b) Castration any age
 - (c) Natural climacteric
 - (d) Ovarian agenesis
 - (2) Follicle stimulating hormone
 - (a) Irreversible state with LH deficiency
 - (b) Tubular disease
 - (c) Castration
 - (d) Natural climacteric
 - (3) Luteinizing hormone—tubular disease with inhibin deficiency
 - c. Thyrotropic hormone
 - (1) Possible in 2a above
 - (2) After thyroidectomy
 - (3) Primary myxedema
 - (4) Postulated in thyroid hyperfunction
 - (5) Exophthalmic syndrome
 - d. Adrenocorticotrophic hormone
 - (1) Predominance of "S" hormones, i.e. Cushing's syndrome
 - (2) Predominance of "N" hormone
 - (a) Adrenogenital syndrome
 - (b) Pseudohermaphroditism
 - (3) Both factors possibly increased in 2a above
- C. CLINICAL**
1. Panhypopituitarism
 - a. Prepuberal
 - (1) Frohlich's syndrome
 - (2) Loran-Levi infantilism
 - (3) Other syndromes

- b Midpuberal
- Postpuberal
 - (1) Simmonds' disease
 - (2) Sheehan's disease
- 2 Selective or predominate deficiencies
 - a Hypogonadotropic hypogonadism
 - (1) Prepuberal
 - (2) Midpuberal
 - (3) Postpuberal
 - b Pituitary myxedema
 - c Pituitary adrenocortical insufficiency
 - d Prepuberal growth and gonadotropic deficiencies (transient)
- 3 Diabetes insipidus
- 4 Gigantism
- 5 Acromegalic gigantism
- 6 Acromegaly
- 7 Cushing's syndrome (basophilism)
- Mixed syndromes
 - a Pituitary dwarfism followed by gigantism
 - b Fugitive acromegaly and hypopituitarism
- D TUMORS
 - 1 Adenoma
 - a Chromophobic
 - b Eosinophilic
 - c Basophilic
 - d Mixed
 - 2 Craniopharyngioma
 - 3 Miscellaneous

XI CHIEF CLINICAL FINDINGS OF HYPOSECRETION

- A INTRODUCTION
 - 1 Separate clinical entities do not exist for each hormone although theoretically possible adequate evidence is not available
 - 2 The reader is referred to predominant or selective hypofunction under
 - a Hypopituitarism—see 6, 7
 - b Hypogonadism—see 47 XVI B 2 61 II E 3, 4 65 VIII
- B GROWTH HORMONE—Growth and somatic development are retarded
- C GONADOTROPIC HORMONES
 - 1 Gonadal hypoplasia
 - a Amenorrhea
 - b Aspermatogenesis
 - Sexual function lost

- 2 Symptoms as in
 - a Hypogonadotropic hypogonadism
 - b Panhypopituitarism
- D THYROTROPIC HORMONE
 - 1 Thyroid hypoplasia—low basal metabolic rate as in hypopituitarism
 - 2 Idiopathic myxedema—possible, but unproved
- E ADRENOCORTICOTROPIC HORMONE
 - 1 Adrenal hypoplasia
 - 2 Symptoms as in hypopituitarism
 - Hypotension
 - b Alopecia of body and sexual hair
 - Asthenia
 - d Hypoglycemia
 - e Anemia
- F LACTOGENIC HORMONE—Agalorrhea
- G PARATHYROTROPIC HORMONE—Idiopathic atrophy of parathyroids, if existence of hormone is proved
- H POSTERIOR LOBE HORMONES—Polyuria and polydipsia as in diabetes insipidus but other factors may exert an influence (see 8 XI B 2, 3)

XII CHIEF CLINICAL FINDINGS OF HYPERSECRETION

- A INTRODUCTION
 - 1 Attempts to assign a role to each hormone in cases of hyperfunction is not yet possible and perhaps never will be, since isolated hormones do not necessarily represent the products secreted by the gland
 - 2 However, certain effects such as those produced by growth and adrenocorticotrophic hormones have fairly typical clinical signs
- B GROWTH HORMONE—Skeletal and tissue overgrowth as in gigantism and acromegaly
- C GONADOTROPIC HORMONES
 - 1 Hyperplasia and hyperfunction of Leydig cells as occasionally found in acromegaly
 - 2 Result of castration, male or female
 - 3 Relationship to climacteric symptoms is not definitely established
- D THYROTROPIC HORMONE
 - 1 Thyroid hyperplasia or hypertrophy
 - a Graves's disease with or without exophthalmos, but proof ■ lacking

- Acromegaly—hypertrophy may be partly due to growth hormone
- 2 Exophthalmos in
 - a Exophthalmic syndrome
 - b Myxedema, acquired
- E ADRENOCORTICOTROPIC HORMONE
 - 1 Adrenal cortical hyperplasia and/or hyperfunction
 - 2 'S' hormones in Cushing's syndrome probably cause
 - a Diabetes
 - b Hypertension
 - Hypertrichosis
 - d Buffalo obesity
 - Striae
 - f Other signs
 - 3 Virilization of females from "N" hormone in
 - a Pseudohermaphroditism
 - b Adrenogenital syndrome
 - 4 Precocious puberty in males due to 'N' hormone
- F LACTOGENIC HORMONE
 - 1 Lactation as noted in
 - a Normal nonpregnant females
 - b Acromegalics
 - 2 Cause of prolonged postpartum lactation possibly
- G PARATHYROTROPIC HORMONE—Idiopathic hyperplasia and hyperfunction of parathyroids, if hormone exists, example, acromegaly
- H CARBOHYDRATE FACTORS
 - 1 Identical with adrenocorticotrophic hormone, probably
 - 2 Diabetes as associated with acromegaly may be due to insular exhaustion from unknown factors (possibly growth hormone)
 - 3 Diabetes which is insulin resistant, as in Cushing's syndrome
- I POSTERIOR LOBE HORMONES
 - 1 Clinical effects are not proved
 - 2 Role has been postulated in
 - a Toxemias of pregnancy
 - b Hypertension
 - c Idiopathic edema

XIII EXAMINATION OF PATIENT

- A COMMENT—The data below are for the most part listed elsewhere but are assembled here as a convenient guide to diagnosis of pituitary dysfunction

B HISTORY

- 1 Hyposecretion
 - a Prepuberal
 - (1) Dwarfism
 - (2) Failure of pubescence
 - (3) Mental alertness
 - (4) Headache
 - b Postpuberal
 - (1) Amenorrhea
 - (2) Libido is lost
 - (3) Headache
 - (4) Visual disturbance
 - (5) Postpartum hemorrhage or shock
 - (6) Pallor
 - (7) Asthenia
- 2 Hypersecretion
 - a Growth factor chiefly
 - (1) Prepuberal—gigantism
 - (a) Height and growth rate are abnormal
 - (b) Sexual development is usually retarded
 - (2) Postpuberal—acromegaly
 - (a) Acral parts enlarged
 - (b) Facies coarsened
 - (c) Visual damage
 - (d) Other special sense impairments
 - (e) Gonadal disorders
 - (f) Sweating
 - (g) Palpitation
 - (h) Headache
 - (i) Polyuria
 - (j) Polydipsia
 - b Adrenocorticotrophic factors mainly
 - (1) Prepuberal
 - (a) Weight gain is rapid (buffalo type of obesity)
 - (b) Growth retardation
 - (c) Acne
 - (d) Purplish striae
 - (e) Hirsutism
 - (f) Sexual retardation
 - (2) Postpuberal
 - (a) Weight gain is rapid (buffalo type of obesity)
 - (b) Acne
 - (c) Purplish striae
 - (d) Hirsutism
 - (e) Amenorrhea
 - (f) Hypertension symptoms
 - (g) Diabetes

C PHYSICAL STATUS—Especially check

- 1 Weight
- 2 Height
- 3 Bodily contours
- 4 Enlargement of acral parts
- 5 Skin for
 - Texture
 - b Moisture
 - c Acne
 - d Purplish striae
 - e Ecchymoses
- Hair growth
- 7 Facial features
- 8 Visual fields, acuity
- 9 Thyroid gland enlargement
- 10 Blood pressure
- 11 Pulse rate
- 12 Genitalia—external and internal
- 13 Tremor

D LABORATORY DATA

(Note The relative significance of the various tests can be judged under the description of each syndrome)

- 1 Urine (routine)
- 2 Hematology
 - a Red blood cells
 - b Hemoglobin
 - c Hematocrit
 - d White blood cells
 - Differential count
- 3 Blood chemical analyses (fasting)
 - a Sugar
 - b Phosphorus (inorganic)
- 4 Function tests
 - a Tolerance
 - (1) Glucose—see 103 I J 1
 - (2) Insulin—see 103 I J 2
 - (3) Glucose insulin—see 103 I J 3
 - (4) Creatine—see 103 V A 9
 - b Adrenal water—see 39 XIII A 5 a
 - c Total eosinophilic count—see 39 XIII A 5 b
 - d Epinephrine injection—see 39 XIII A 5 b
 - e Adrenocorticotropin injection—see 39 XIII A 5 c
- 5 Miscellaneous test—basal metabolic rate—see 14 XIII D 3
- 6 Urinary hormone assays
 - FSH—see 106 I B 1
 - b Estrogens—see 107 V A C
 - c 17 ketosteroids—see 107 III A D
 - d 11 oxysteroids—see 107 IV A D

7 Vaginal smears for estrin effect—see 57 XIII E 2

E METHODS FOR SPECIAL PROCEDURES

1 Diabetes insipidus

■ Salt loading

(1) Intravenous³

- (a) Indication—to differentiate between diabetes insipidus and psychogenic polydipsia and polyuria

(b) Method

- [1] Antidiuretic therapy ■ stopped prior to procedure to allow for a return of symptoms
- [2] Fluids restricted for 8 hrs preceding test
- [3] Water taken by mouth 20 cc/kg within 1 hr
- [4] Indwelling catheter is inserted $\frac{1}{2}$ hr after bydration is started
- [5] Urine specimens are collected every 15 min
- [6] Output is calculated in cc/min
- [7] An infusion of 2.5 per cent sodium chloride is given intravenously after 2 control periods with an adequate urinary excretion (over 5 cc/min)
- [8] Solution is given at a rate of 0.25 cc/kg/min for 45 min
- [9] Pitressin, 0.1 unit, is given intravenously if no decrease in urine flow is noted during first 2 postinfusion periods or during infusion

(c) Results in urine flow during and after infusion

- [1] Normal—decreased
- [2] Abnormal—continued diuresis prompt decrease following pitressin

(2) Oral^{7 8}

- (a) Indication—aid in diagnosis of diabetes insipidus
- (b) Method
 - [1] Breakfast omitted

[2] Patient given 0.25 Gm of sodium chloride/kg of body weight as a 10 per cent aqueous solution

[3] The following are determined before beginning the test and at hourly intervals for 5 hrs

[a] Blood serum chloride as sodium chloride (mg %)

[b] Urine chloride as sodium chloride (mg/min)

[c] Total urine excreted (cc/min)

(c) Results

[1] Normal

[a] Sodium chloride concentration rises in serum and urine

[b] Urinary minute output—unchanged

[2] Diabetes insipidus

[a] Sodium chloride concentration serum—rises urine—concentration remains very low

[b] Urinary minute output—moderate rise

b Low salt ingestion^{7, 8}

(1) Indication—test for effect on polyuria in diabetes insipidus

(2) Method—approximately 1.5 Gm of sodium chloride allowed per day

(3) Results

(a) Normal—no changes

(b) Diabetes insipidus—urinary volume and chloride concentration decreased

c Water deprivation^{9, 10}

(1) Indication—to determine effect on polyuria in diabetes insipidus

(2) Method

(a) Fluid intake restricted as long as possible usually 24 hrs

(b) Diabetes insipidus patients may not be able to stand thirst variable symptoms may develop

(3) Results

(a) Normal

[1] Total output less than intake

[2] Specific gravity is high

(b) Diabetes insipidus

[1] Total output exceeds intake

[2] Specific gravity rarely over 1.010¹⁰

2 Cushing's syndrome

a Sodium chloride excretion

(1) Indication—aid in diagnosis of adrenocortical hyperfunction

(2) Method

(a) Basic diet (3 days) containing

[1] Chloride 0.95 Gm

[2] Sodium, 0.59 Gm

[3] Potassium, 4.06 Gm

(b) First day

[1] Fluid intake is limited to 20 cc/kg of body weight

[2] Sodium chloride, 10 Gm in capsules in morning and with supper

(c) Second day—repeat as for first day

(d) Third day

[1] Bladder emptied at 8 A.M.

[2] Urine collected from 8 A.M. to 12 noon (4 hrs)

[3] Before 11 A.M., 5 cc of fluid/kg of body weight is given

(e) Amount of chloride in urine specimen is determined

(3) Results

(a) Normal—over 400 mg % of urinary chloride

(b) Decreased amounts

[1] Adrenocortical hyperfunction

[2] Renal concentration impairment

[3] Pregnancy possibly

b Paradoxical excretion of sodium chloride with desoxycorticosterone¹¹

(1) Indication—may be valuable in diagnosis of hyperfunction of adrenal cortex

(2) Method

- (a) No food during the test
- (b) Fluids are restricted after 7 P.M. the night before procedure
- (c) At 6 A.M., patient voids and urine is discarded
- (d) 500 cc. of water taken
- (e) All urine is saved from 6 to 9 A.M. (first specimen)
- (f) At 9 A.M., 200 cc. of 5 per cent saline (10 Gm salt) injected intravenously
- (g) Second specimen of urine saved from 9 A.M. to 12 NOON
- (h) Two days later, same procedure is repeated
- (i) Previous evening at 10 P.M., 10 mg. of desoxycortico sterone acetate given intramuscularly
- (j) Volume of each urine specimen determined and carefully noted
- (k) Sodium and chloride are analyzed in each urine specimen
- (l) Total urinary sodium and chloride ions excreted in first specimen are subtracted from the second (period after the intravenous injection)
- (m) This figure represents the excess over the basal excretion of these ions
- (n) Value in milliequivalents divided by 171 (i.e. milliequivalents in 10 Gm. of sodium chloride) yields the fraction of the injected ions excreted
- (o) Comparison of results obtained during the control period and that after the injection of desoxycortico sterone acetate (DOCA) gives the percentage of increased excretion or retention caused by the use of the hormone

(3) Results

- (a) Normal—decrease in urinary excretion of sodium and chloride ions
- (b) Cushing's syndrome—increase

3 Protein metabolism

a Amino acid (blood) response¹

- (1) Indication—utilization of amino acid may be determined, but to a certain degree only

(2) Method

- (a) Gelatine, 50 Gm. in 500 cc. of water is given to a fasting subject
- (b) Mixture taken again in 3 hrs
- (c) Blood samples fasting, 1, 2 and 3 hrs
- (d) Amino acids are calculated in mg. %

(3) Interpretation

(a) Normal

- [1] First administration—marked rise
- [2] Second administration—slight or no increase

- (b) Pituitary insufficiency—results of second concentration are high or even above the first

- (c) Pituitary dwarfism—normal response

- (4) Comment—test has been used to show that protein metabolism factor is not identical with growth hormone

b Specific dynamic action of protein (S.D.A.) (see 103 IV H)^{1 4}

(1) Indications

- (a) Study of response to ingested proteins by determining effect on basal metabolic rate

- (b) Experimental purposes

(2) Method

- (a) Initial basal metabolic rate is taken after 14 hrs. of fasting

- (b) Patient ingests 3 boiled eggs or 200 Gm. of boiled chopped beef with a slice of toast and 100 cc. of water

(c) Basal metabolic rate ■ repeated in 2 hrs, during which time the patient remains resting in a reclining position

(3) Results

(a) Normal—rate is increased by 14 to 18 per cent

(b) Endocrine diseases—normal in majority (see specific chapters)

(c) Simple obesity—may be decreased

(d) Undernutrition—may be increased

F ROENTGENOGRAPHIC FINDINGS

1 Skull for

a Sella enlargement (see below)

b Other abnormalities

2 Hand wrist for bone age

3 Bone texture in

a Lumbosacral spine

b Pelvis

4 Flat plate of abdomen and/or air in suflation

5 Arteriography (see Figs 25, 26)

a Indications—should be judged by competent neurosurgeon

b Purpose—arteriography (first introduced by Moniz⁹) is

(1) Means for visualizing intracranial aneurysms

(2) Useful in differential diagnosis of tumors in or about the sella turcica (see 2 XIV H)

c Data suggesting aneurysm¹⁴

PER CENT

(1) Subarachoid hemorrhage 75

(2) Cranial nerve involvement 46

(3) Headache
(a) Generalized 40
(b) Unilateral 43

(4) Facial pain 7

(5) Convulsions 10

(6) Vertigo 10

(7) Hypopituitarism and myxedema 3

(8) Roentgen evidence suggesting aneurysm—thinning of lateral margin of optic foramen (see 2 XIV H 1, Fig 26)⁸

d Technique¹⁴

(1) All patients should be tested for sensitivity to iodine because diodrast is used

(2) Selection of side to inject is often possible from

(a) History

(b) Physical signs

(3) Closed method of injection

(4) Pentothal anesthesia (following encephalogram)

(5) Patient

(a) Is kept on carrier stretcher which is made immobile

(b) Lies on back, with pillow under shoulder blades and with two Turkish towels under occiput

(6) Needle (2 in, 18 gauge) is

(a) Attached to 20 cc Luer Lok syringe with 2 way stop cock containing citrate solution

(b) Directed to penetrate adventitia from 1 to 2 cm below bifurcation of common carotid artery

(7) Several injections of citrate solution are made to ensure free flow, with needle well in and directed toward lateral wall of artery

(8) Syringe with 20 cc of diodrast is connected

(9) Preparations made for roentgen exposures, using upright automatic Bucky for stereoscopic views

(10) Fifteen cc of diodrast injected rapidly

(11) First roentgen exposure made

(12) Remainder of solution (5 cc) given during automatic shifting of roentgen tube

(13) Second exposure taken

6 Ventriculography^{5, 13}

a Indication—localization of tumor extension of pituitary adenomas

b Method

(1) Burr opening 3.5 cm on both sides midline in parieto occipital region after proper preparation

(2) Dura is opened

- (3) Avascular portion of cortex is exposed
 - (4) Arachnoid is punctured with pointed knife
 - (5) Ventricular needle is inserted into each ventricle
 - (6) Fluid is allowed to escape
 - (7) It is replaced by volume of air less than amount removed
 - (8) Soft rubber No. 8 catheter is inserted into ventricle through track of ventricular needle which contained most fluid
 - (9) Scalp is sutured, and catheter is tied in place with black silk thread which was used to close incision
 - (10) Catheter is occluded near scalp with silver clip
 - (11) Cut end of catheter is attached to black silk thread used to close scalp incision on opposite side
 - (12) Wound is covered with small gauze dressing
 - (13) Roentgen studies are then made taking anterior, posterior and lateral stereoscopic views
 - (14) More air can be inserted if ventricular system is incompletely filled
 - (15) Patient is returned to operating room when roentgen plates have been interpreted
 - (16) Catheter is opened, permitting air and fluid to escape and is allowed to drain preventing subsequent cortical bulging and better circulation
 - (17) Craniotomy if indicated
- b Anterior and posterior clinoids may be fused on one or both sides, thus bridging the sella, which is of no clinical significance
 - c The anterior clinoids when viewed laterally in roentgen films form a partial roof over the anterior portion of the sella, the posterior clinoids may do the same
- 3 The optic chiasm
 - a Lies upward and anteriorly to
 - (1) Tuberculum sellae
 - (2) Anterior clinoids
 - b May be compressed by a pituitary or another tumor in this region
 - 4 Internal carotid arteries
 - a Location—pass lateral to the dorsum sellae, then wind upward and medial to the anterior clinoids
 - b In this area the arteries are somewhat inferior and posterior to the optic nerves
 - c Aneurysms of these arteries may distort and erode the clinoid processes and the floor of the optic nerve
 - 5 The sphenoid sinus lies anterior and inferior to the sella turcica; pituitary tumor may depress floor of sella into sinus
 - 6 The sixth cranial nerve lies lateral to the internal carotid artery and may be impinged upon by pressure from an aneurysm rarely if ever with pituitary adenoma

B AVERAGE MEASUREMENTS IN ROENTGENOGRAMS (see Chart 11)

- 1 Depth and anteroposterior diameter of lateral contour^{7 1 10 0 4 8 36 41}

	MM
a Birth	25 x 3
b One year	4 x 5
c After 1 year gradual increase to	9 x 11
d Over 18 years	Variations are marked

- 2 Area of lateral contour in square millimeters (Haas method)^{4 15 17 20 23 27 43}

	SQ MM
a Birth	12
b At 3 years rather rapid increase to	48
c Between 20 and 25 years levels off to	74

XIV THE SELLA TURCICA

A CLINICAL IMPORTANCE OF CERTAIN ANATOMIC FEATURES (see Fig. 24)

- 1 Roentgenologic observation of the sella turcica should be made in all cases of suspected or definite pituitary disease
- 2 Clinoid processes (see Fig. 25)
 - a Their position varies, but both (anterior and posterior) pairs usually point in a similar direction and any change in this respect may indicate pressure (see below)

- 3 Dorsum—0.11 mm to 0.20 mm
- a Birth 6.75
- b At 10 years, increases to 7.5
- c Adulthood 12 to 18
- C RELATIONSHIP OF SELLA TO SIZE OF SKULL
- 1 Skull at birth is approximately two thirds of its adult size
- 2 Increase in size of sella with growth is relatively much greater than that of the skull
- 3 Size of skull is not a suitable standard for comparison of sella size
- D VOLUME AND WEIGHT
- 1 Average volume of sella turcica as compared with volume displaced by hypophysis³¹
- a Sella (denuded of all tissues, based on measurements of 70 cadavers)—120 cc
- b Hypophysis—0.57 cc
- c Range for either—0.75 to 2.0 cc
- 2 Estimated volume from roentgenologic measurements
- a Attempts to estimate volume of sella by measurements of lateral contour area and width of dorsum (Kovacs⁵) are said to correlate with injection methods in the cadaver but confirmatory evidence is needed
- b Efforts to determine a more constant estimate of sella size in relation to age sex and height by measurements of floor, dorsum, in trichiloid spaces lateral contour areas as well as depth anterior and posterior diameters have been disappointing^{17 34}
- c Even if the sella volume could be measured accurately from roentgenograms the size of the hypophysis would remain unknown because
- (1) An enlarged sella does not always contain a corresponding increase in size of the pituitary gland²
- (2) Considerable hypertrophy of the gland may take place before the sella increases in size²⁰
- (3) Tumors may grow out through diaphragm without affecting the size of the sella¹⁷
- 3 Average weight of hypophysis^{3 3 3}
- mm 0.31 mm 40
- gm
- a Birth (variations 0.05 to 0.1) 0.1
- b 7 years 0.5
- c 25 to 45 years (variations 0.3 to 0.5) 0.6
- d 45 years and over 0.5
- F HEIGHT AGE AS A STANDARD FOR SIZE OF LATERAL CONTOUR AREA²
- 1 The sella increases with age in normal children
- 2 Height age (i.e., normal average height for a given chronologic age as shown by height charts) is a good index of somatic and skeletal development in the normal as well as in the abnormal, with the exception of chondrodystrophy
- 3 Chondrodystrophy—sella is
- a Normal average size for any given chronologic age
- b Relatively large for height age thus the latter cannot be used as an index
- 4 Dwarfs without pituitary, suprasellar tumors or intracranial pressure—the sella is often smaller than would be expected for height age (see Protocol 3 IV)²²
- 5 Cretins
- a The sella is large for height age as well as for chronologic age in some cases (see 24 VIII A 1)²²
- b This confirms the findings of enlarged pituitaries at postmortem¹⁹
- 6 Hypertension—Ziskin reports larger sellas than normal¹³
- 7 Trends are most likely to be manifested in a series rather than in individual cases
- F MEASUREMENT OF LATERAL CONTOUR AREA
- 1 Introduction
- a A more accurate measurement of contour area than the use of 2 diameters (AP and depth)
- b Changes in size from time to time may be more easily detected
- c Areas may be estimated in most cases by the use of the sellameter, which eliminates outlining the contour on transparent paper (see Chart 12)

- 2 *Technic of measuring lateral contour areas by method of Haas*²⁰
 - a Stereoscopic films are necessary
 - b Tuberculum sella and tips of posterior clinoids are identified, and the midpoint between the latter on the upper dorsum is marked
 - c A line is drawn between the tuberculum sella and midpoint of the posterior clinoids
 - d The lateral contour ■
 - (1) Outlined on the film with a fine pointed grease pencil
 - (2) Traced upon semitransparent sq mm ruled paper
 - (3) Sketched directly on the paper if the inner border of the sella is distinct
 - e Squares are counted
 - f If the right and the left contours differ in size, the two areas are outlined
 - g Unilateral enlargement is not uncommon from aneurysm and tumor
- 3 Measurements of width of dorsum, in clinoid spaces and floor of sella are helpful in special cases, as unilateral tumors with or without erosion¹⁸

G INTERPRETATION OF VARIATIONS IN SIZE OF LATERAL CONTOUR AREAS

- 1 Since enlargement of the sella does not necessarily mean the presence of a tumor, no definite measurements may be cited which would ensure the diagnosis of pituitary tumor
- 2 Pituitary tumors of clinical significance may be present without enlargement of the sella but this is rare
- 3 Of 1000 pituitary glands examined at postmortem, adenomas were found from 1 mm up to a size which occupied the entire sella yet none was considered clinically significant⁶
- 4 Areas
 - a To 150 sq mm—not uncommonly found without evidence of pituitary dysfunction or pressure
 - b Above 150 sq mm—usually indicate pituitary tumor, frequently with clinical signs and/or symptoms
- 5 Enlargement of the sella may occur without pituitary tumor in
 - a Cretinism

- b Suprasellar cyst
- c Women past 40 years of age who have been castrated before 25 years of age⁴⁴
- d Hydrocephalus
- e Chronic increased intracranial pressure from any cause
- f Hypertension⁴⁵
- 6 Procedures for problem of enlarged sella found unexpectedly on roentgenography of skull
 - a Careful inspection for other abnormalities of skull (see below)
 - b Clinical appraisal for hormonal changes of hyper or hypopituitarism
 - c Visual field examination for evidence of optic nerve pressure
 - d Headache
 - (1) If persistent and impressive roentgen therapy may be tried
 - (2) Avoid informing the neurotic patient of 'tumor in the head' and defer roentgen therapy
 - (3) Re examine at later date for further enlargement and other unusual findings

H OTHER ROENTGENOGRAPHIC OBSERVATIONS ON THE SELLA¹⁸ (see Fig 26)

- 1 Abnormal position or calcium content of anterior clinoids
 - a Unilateral elevation of 1 anterior clinoid with erosion—typical of an aneurysm
 - b Bilateral elevation—intrasellar lesion
- 2 Abnormal position, decreased calcium content or destruction of posterior clinoids—intrasellar or suprasellar lesion
- 3 Depression and thinning of floor into sphenoid sinus—frequent in pituitary adenomas
- 4 Suprasellar calcification—suggestive of suprasellar tumor
- 5 Intrasellar calcification—may represent old infarction or inactive tumor
- 6 Calcification of internal carotid arteries, as shown by calcium deposits lateral to anterior clinoids—indicate arteriosclerosis
- 7 Abnormalities of skull which may indicate hyperpituitarism
 - a Sinus enlargement
 - b Prognathism
 - c Texture of tables

- 8 Encephalograms reveal extension of pituitary tumor
 - a Upward distention of capsule into suprasellar space
 - b Laterally

- 9 Arteriograms show arterial aneurysms causing unilateral enlargement of sella turcica simulating an intrasellar tumor (see 2 VIII F 5)

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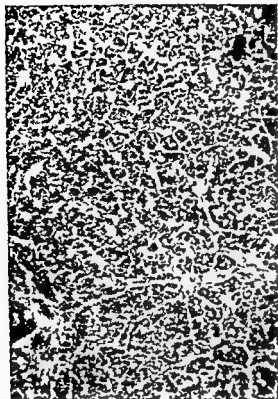


FIG 22 PITUITARY GLAND Normal anterior pituitary gland in an adult male. Note sinusoidal arrangement of cells (x 72)



FIG 23 MALIGNANT ADENOMA OF THE ANTERIOR PITUITARY. Section from a partially removed tumor in an underdeveloped 15 year-old boy who complained of head ache. Weight 83 lbs. Height 58 in. Bone age 17 years. Large sella turcica (2.5 sq mm). Complete blindness in left eye. Quadrant defect in right. Recurrence of symptoms several months after operation. Marked improvement with roentgen therapy. Note the large cells with multiple or very large nuclei and occasional mitoses.

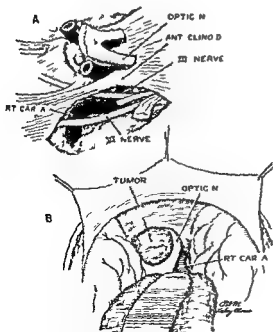


FIG 24 ANATOMY OF THE SELLAR AREA (A) Anatomic relationships of optic chiasm, third and sixth cranial nerves, and internal carotid arteries to sella turcica are illustrated. The cut stalk of the pituitary gland is seen under the chiasm. (B) An expanding pituitary tumor is shown spreading the chiasm. Note position of right carotid artery (A and B) and the potentialities of pressure phenomena with an aneurysm. One effect detectable only in roentgenograms of optic foramina is erosion of the floor under the optic nerve between the anterior clinoid and the dorsum sellae.

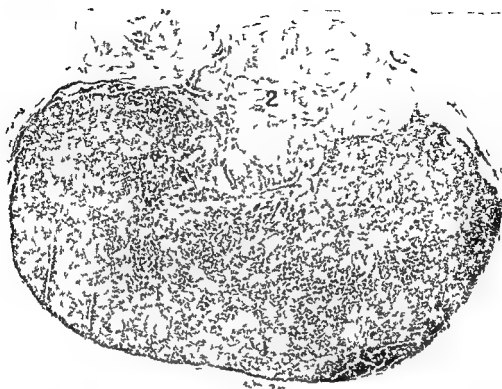


FIG 20 ADULT PITUITARY GLAND Horizontal section ($\times 78$) showing relative size of anterior (1) and posterior (2) lobes (S P Hicks and W A Meissner)

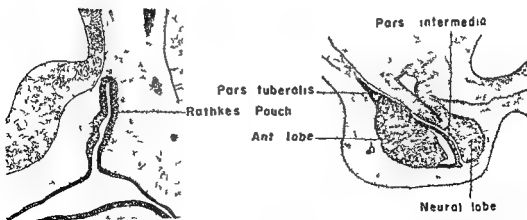


FIG 21 EMBRYOLOGIC DEVELOPMENT OF THE PITUITARY (Left) sagittal section through hypophysis region of a 10.5 mm human embryo Nasal end at left (Right) Sagittal section through hypophysis region of a 55 mm human embryo Nasal end at left (Atwell W J The development of hypophysis cerebri in man with special reference to pars tuberosa Am J Anat 37 159)

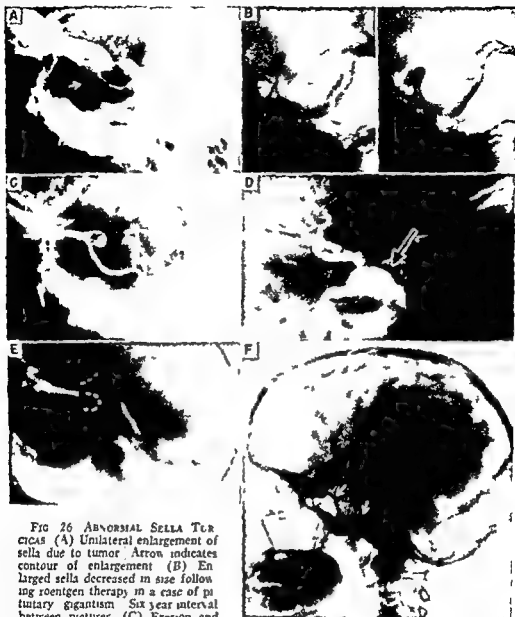


FIG 26 ABNORMAL SELLA TURCICAS (A) Unilateral enlargement of sella due to tumor. Arrow indicates contour of enlargement (B) Enlarged sella decreased in size following roentgen therapy in a case of pituitary gigantism. Six year interval between pictures (C) Erosion and nonvisualization of one anterior clinoid process (arrow) due to aneurysm verified by arteriogram (D) Arteriogram demonstrating aneurysm of internal carotid artery which eroded one anterior clinoid (C) (E) Elevation of anterior clinoid due to aneurysm (F) Enlargement of sella with erosion and nonvisualization of all clinoid processes due to chronic internal hydrocephalus. Note also scalloping of skull due to chronic pressure.

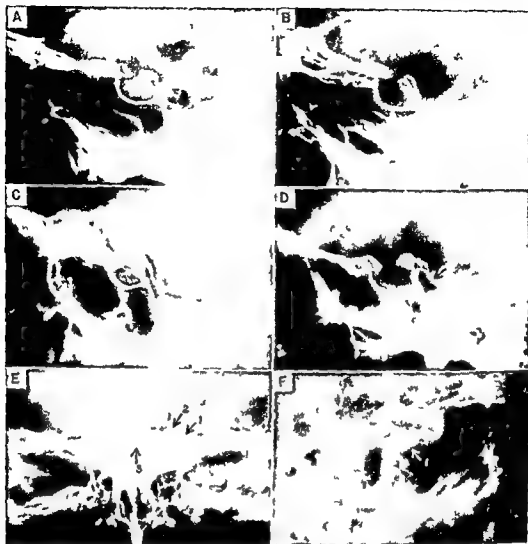


FIG 25 NORMAL SELLA TURCICAS AS SHOWN BY ROENTGENOGRAPHY (A) Lateral view of a normal sella (B) Slightly oblique view (other film of stereoscopic set) showing both anterior and posterior clinoid processes (C) A bridged sella is of no endocrine significance (D) Calcification of petroclinoid ligament (arrow) a normal finding when present (E) PA view showing anterior clinoids (1) dorsum and posterior clinoids (2) and planum sphenoidale (3) (F) Arteriogram of a normal skull (1) floor of sella (2) internal carotid artery

PITUITARY—CLINICAL

HYPOPITUITARISM

INTRODUCTION

I DEFINITION

GENERAL—A deficiency or absence of one several or all hormones of the anterior lobe of the hypophysis

II CLINICAL (HORMONAL) CLASSIFICATION

A INTRODUCTION

- 1 Different combinations of hormonal deficiency may exist
- 2 Intermediate syndromes between well defined clinical types are possible
- 3 Hypersecretion of several factors may be found in presence of hyposecretion of others i.e. pituitary gigantism

B PREPUBERAL ANTERIOR PITUITARY DEFICIENCIES

- 1 Apituitarism (panhypopituitarism)
 - a Complete absence of anterior pituitary hormones
 - b Example—Simmonds disease
- 2 Hypopituitarism
 - Essentially a reduction in all anterior pituitary hormones
 - b The difference between hypopituitarism and apituitarism is chiefly a matter of degree and cannot always be determined in any one case
 - The following syndromes consist mainly of gonadotropic and growth hyposecretion with a lesser deficiency of other pituitary hormones
- d These conditions are closely allied if not identical
 - (1) Pituitary dwarfism (see Figs 29 and 30)
 - (2) Frohlich's syndrome (adiposogenitodystrophy (see Fig 27))
 - (3) De la Cour-Lorain-Levi infantilism (see Fig 28)^{20 7}
 - (4) Ateliosis (Greek derivative)

(5) Nanism (Latin derivative)²⁸

(6) Patau's dwarfism⁹

e Growth and gonadotropic hypofunction

- (1) Retarded growth and hypogonitalism without evidence of other hormonal deficiency occur occasionally
- (2) Undoubtedly, these cases might be classified under above syndromes (see 5 \ I)

3 Hypogonadotropic deficiencies

- a Hyposecretion of one or both of the following
 - (1) Follicle stimulating hormone (FSH)
 - (2) Luteinizing hormone (LH)
- b Examples (all may be transient with eventual recovery)
 - (1) FSH deficiency—eunuchoidism
 - (2) FSH and LH deficiencies—eunuchoidism
 - (3) LH deficiency—adiposogenital dystrophy or hypogonitalism (as described by McCullagh⁶⁴)

C POSTPUBERAL ANTERIOR PITUITARY DEFICIENCIES

- 1 Apituitarism
 - a Complete absence of all the anterior lobe hormones
 - b Example—Simmonds disease
- 2 Hypopituitarism—hypofunction involving most or all anterior pituitary hormones
- 3 Unihormonal deficiencies predominantly
 - a Hypogonadotropic — FSH and/or LH deficiency (see 45 \ B 3 47 \ I)
 - b Pituitary myxedema (hypothyrotropic deficiency) (see 6)
 - c Pituitary Addison's disease (hypoadrenocorticotrophic deficiency) (see 7)

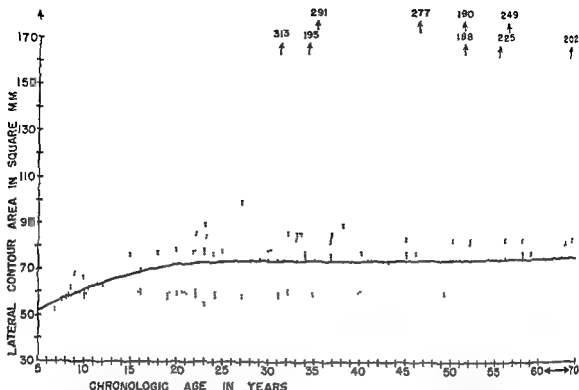


CHART 11 MEASUREMENT OF LATERAL AREAS OF SELLA TURCICAS Distribution according to size and age of 671 consecutive roentgenograms. A large number were measured by contour including all those before 10 years of age which proved to be too tedious. The rest were estimated by sella meter. This accounts for the tendency of the results to fall into groups. The dots with numbers and arrows were well above 1.0 sq mm and represented for the most part tumors which were clinically significant. The black line indicates averages for each 5 year group. The wide variation is to be noted. (From unpublished data of Drs Hare H F, Newcomb R B, Taft G H, Saltzman F A, Silveus E, Musulin N and Huxthal L M.)

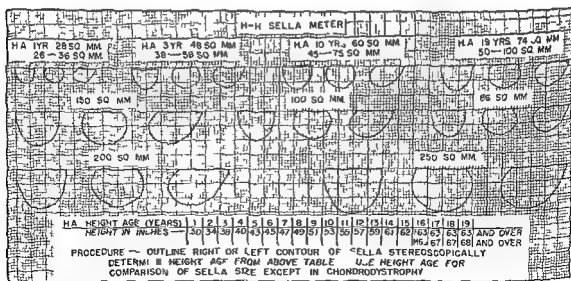


CHART 12 SELLA METER Average lateral contour areas at different ages. The above arrangement is used for determining quickly the size of sella when imprinted on transparent cellophane (known as the sella meter-Huxthal & Hare. May be procured from Ansco Binghamton N Y) (Hare H F, Silveus E and Smedal M I. Roentgen Diagnosis of Pituitary Tumor Radiology 52 193)

2	Hair	
a	Head	Fine sparse or abundant
b	Facial	None
■	Axillary	Absent or slight amount, delayed in appearance
d	Pubic	Absent or slight amount delayed in appearance
e	Body	Variable
F	HEAD	
1	Shape and size	Proportionate to body size
2	Facial expression	Infantile except late in disease
3	Eyes	
a	General	Normal, occasionally ptosis and/or ophthalmoplegia squint ¹⁵
b	Fundi	Normal papilledema or optic atrophy ⁷
■	Visual	
(1)	Fields	Normal or restricted if tumor ■ the cause (craniopharyngioma) ²³
(2)	Acuity	Normal unless tumor pressure, may have complete loss
4	Ears and nose	Proportionate to face smell may be impaired or absent
5	Mouth and throat	
a	General	Normal
b	Teeth	Normal ⁴⁰ may have widely spaced upper incisors and abnormal development of lateral incisors, delayed decidual extrusion
G	NECK	
1	General	Proportional to build
2	Thyroid	Barely palpable if at all
H	CHEST	Narrow miter shaped ⁷
I	HEART AND PERIPHERAL VESSELS	
1	Heart	Not remarkable may be hypoplastic
2	Rate and rhythm	Normal or bradycardia
3	Blood pressure	Normal or slightly decreased ^{1 31 4 7}
4	Peripheral arteries and veins	Normal
5	Vasomotor	See skin
J	BREASTS	
1	Male	Normal no actual primary gynecomastia
2	Female	Underdeveloped
K	ABDOMEN	Often potbellied ³⁷
1	Liver	Not palpable (see 92 V D 2a)
2	Spleen	Not palpable
3	Hernia	None
4	Tumor	None
L	GENITALIA	
1	Male	
a	Penis	Small
b	Testes	Small or undescended flabby consistency but may feel normal for developmental stage ^{39 5 67 70 8}
■	Prostate	Small
2	Female	
a	External	Retarded
b	Internal	Atrophic

SECTION 3

PREPUBERAL HYPOPITUITARISM

I DEFINITION	A condition resulting from diminished secretion of the anterior pituitary hormones (hypopituitarism), generally including all of them, but especially the gonadotropic and growth factors
II APPEARANCE	A well proportioned normal looking individual with retarded growth and sexual development (see Figs 27 30, 34 36, 38 40)
III AGE	Any before puberty
IV SEX	No predominance of either
V MENTAL DEVIATIONS	
A INTELLIGENCE	Normal I Q , occasionally below normal if there is pressure from the pituitary tumor or when associated with a primary mental deficiency ^{4 6 10 14 38 78}
B RESPONSIVENESS	Usually alert, rarely retarded, impish, emotional
C OTHER ABNORMALITIES	No deviation from normal psyche immature, and mild psychoses in some
VI PHYSICAL STATUS	
A NUTRITION	
1 Weight	From undernourished to obese ^{6 78}
2 Fat distribution	Female contours in the male (absence of male sex hormone) not remarkable in females prominent mons pubis especially in male
B HEIGHT	Proportionate dwarfism, final stature dependent on age of onset, duration and rate of growth retardation
C EXTREMITIES	
1 Upper	Proportionate to body size
a Hands	Proportionate to development
b Fingers	Proportionate
c Span	Normal for height
2 Lower	Proportionate to body size
a Feet	Match rest of size
b Toes	Proportionate
D SPINE	Normal
E INTEGUMENT	
1 General	
a Texture	Normal or smooth later wrinkled geroderma nails thin and underdeveloped
b Temperature	Subnormal
c Moisture	Normal or decreased
d Eruptions	None
e Pigmentation	Brown freckles moles hemangiomas frequent
f Color	Eventually pallor

- h Hypoplasia or atrophy with fibrotic sclerosis⁴³ ■
 - i Hemorrhage⁴³
 - j Abscess⁴³
 - 2 Thyroid²⁹ 44
 - Normal
 - Hypoplasia
 - 3 Adrenals
 - a Normal
 - b Hypoplasia⁷⁰
 - 4 Gonads⁸ 49
 - a Normal
 - b Small
 - 5 Thymus⁴⁹ 71
 - Small
 - b Enlarged
 - 6 Cerebral lesions
 - Infundibular tumor
 - b Hydrocephalus⁷⁰
 - c Glioma
 - d Endothelioma
 - 7 Other organs—general splanchnometria
- B Microscopic Pituitary—different lesions see above and 2 IX B¹¹

XI PATHOLOGIC PHYSIOLOGY

- A GROWTH FACTOR
- 1 Hyposecretion rarely ceases
 - 2 Level of serum phosphorus may reflect degree of hormonal function
- B GONADOTROPINS
- 1 Reduction or absence of secretion
 - 2 Retardation and cessation of sexual development
- C THYROTROPIN
- 1 Variable degrees of decreased secretion
 - 2 Mental deterioration of cretinism is rarely observed
- D ADRENOCORTICOTROPIN
- 1 Amount is reduced (by inference)
 - 2 Addisonianlike symptoms are unusual
 - 3 The higher degree of thyroid function in Addison's disease may be responsible for the frequent acute crises in that disease as compared with their uncommon occurrence in hypopituitary states
 - 4 Water test may be positive however there is little evidence of faulty salt metabolism
 - 5 N and S hormones are balanced at a decreased level

- E COMMENT
- 1 General physical and mental activity seem less affected in hypopituitary dwarfs than in adults
 - 2 This may be due to a greater capacity of the endocrine glands to function at a low level independently of the pituitary during childhood (see Protocols 3 I to IV)
 - 3 The following may play a role
 - a Daily caloric intake
 - b Appetite
 - c Utilization of protein⁶⁸
 - (1) Ingestion of gelatine produces a normal rise in blood amino acids in pituitary dwarfs
 - (2) With severe pituitary cachexia on the other hand there is an abnormal rise in blood amino acids suggesting faulty anabolism
 - d Hypothalamic involvement

XII SYMPTOMATOLOGY

- A OF TUMOR AND/OR INTRACRANIAL PRESURE
- 1 Headache
 - a Location
 - (1) Frontal
 - (2) Bitemporal
 - b Vague
 - c Persistent
 - d Severity variable
 - 2 Visual disturbances
 - a Scotoma
 - b Blindness one or both eyes
 - c Amblyopia
 - d Diplopia
 - e Squint
 - f Ptosis
 - g Visual fields
 - (1) Restricted
 - (2) Hemianopsia
 - (a) Unilateral
 - (b) Bilateral
 - 3 Nasal complaints
 - a Anosmia (in some)
 - b Spinal fluid seepage through nose or nasopharynx
 - c Epistaxis
 - 4 Deafness
 - 5 Vertigo
 - 6 Insomnia

M NEUROMUSCULAR

- | | |
|------------------|--|
| 1 Muscles | Not well developed |
| 2 Gait | Matches height, may be ataxic |
| 3 Body movements | Normal, some very graceful others awkward |
| 4 Tremor | None |
| 5 Paresthesias | None |
| 6 Reflexes | Normal may be increased in presence of tumor |

N SPEECH

Normal

VII LABORATORY DATA—see 5 VII**VIII ROENTGENOLOGIC FINDINGS****A SKULL (see Figs 31, 33 and 35)**

- | | |
|-----------------|---|
| 1 Cranial vault | Normal or thin |
| 2 Sella turcica | Normal small or enlarged if tumor or cyst is present, suprasellar calcification possible erosion of clinoids, separated sutures ^{13 1 74 11 20 6 8 87} |
| 3 Mandible | Disproportionate to maxilla ¹³ |
| 4 Sinuses | Poorly developed |
| 5 Teeth | Normal dental age, may be retarded ¹⁰ |

B EPIPHYSEAL STATUS (bone age) Retarded usually at any age may be normal if very recent onset, epiphyses may show necrosis or remain cartilaginous may close late if treated development of osseous nuclei is delayed (see Figs 31 37 and 42)^{1 6 10 14 15 37 39 0 78 81}**C LONG BONES**

Proportionate to body size

D VERTEBRAE

Normal may be osteoporotic

E BONE TEXTURE

Appears normal

F MISCELLANEOUS

Nothing additional

IX ETIOLOGY (see 92 IV V)**A UNKNOWN****B CONGENITAL—Diagnosis by**

- 1 Exclusion
- 2 Family history

C TUMOR (see 3 V)

- 1 Pituitary
- 2 Hypothalamic

D NUTRITIONAL AND/OR METABOLIC CHANGES—Probably action through pituitary in many cases**E TRAUMA^{67 75}****F HYDROCEPHALUS****G INFECTIONS**

- 1 Syphilis
- 2 Meningitis
- 3 Encephalitis
- 4 Others

X PATHOLOGY^{1 4 14 3 38 39 67 70 78}**A GROSS**

- 1 Pituitary^{9 20 51 6}
 - a Normal^{11 7}
 - b Teratoma
 - c Craniopharyngioma (adamantinoma of craniopharyngeal duct) (see Fig 29)^{8 11 17 8 33 9}
 - d Other tumors found
 - (1) Angiomatous⁴⁷
 - (2) Benign chromophobe⁴
 - (3) Basophil adenoma⁵⁴
 - (4) Malignant adenoma (anterior lobe) (see Fig 23)
 - (5) Suprasellar types⁸
 - e Cholesteatoma
 - f Colloid cystic degeneration⁴³
 - g Necrosis may be embolic⁶⁸

- (2) Synonyms
 - (a) Primary hypogonadism
 - (b) Primary hypopituitarism
 - (c) FSH positive eunuchoidism
- (3) Height age—normal
- (4) Bone age is increasingly retarded as age approaches usual time of epiphyseal closure (18 for boys, 17 for girls)

- (5) Growth rate—normal
- (6) Spm
 - (a) Increases over height beginning between the ages of 12 to 14
 - (b) Becomes greater as growth proceeds unless treated
- (7) Breasts
 - (a) Male—may enlarge
 - (b) Female—development may be
 - [1] Absent
 - [2] Slight

- (8) Testes
 - (a) Small
 - (b) Flabby
 - (c) Minuscule
- (9) Amenorrhea (primary)
- (10) Urinary FSH
 - (a) Increased
 - (b) Progressively greater amounts in subsequent years
- (11) 17 ketosteroids
 - (a) Low for age
 - (b) Increased possibly due to adrenal hyperplasia

d True secondary hypogonadism (see 47 VIII 65 VIII)

- (1) Etiology—due to a selective deficiency of gonadotropins and normal secretion of other pituitary hormones
- (2) Synonyms
 - (a) Primary pituitary gonadotropic failure
 - (b) Secondary hypogonadism or hypopituitarism
 - (c) FSH negative eunuchoidism
- (3) Height age—normal
- (4) Bone age—retarded
- (5) Growth rate—normal
- (6) Spm—increased
- (7) Breast development—absent

- (8) Testes
 - (a) Up to the age of 12 or 13 years may be
 - [1] Normal
 - [2] Small
 - (b) After 12 to 13 years—no further enlargement
- (9) Amenorrhea
- (10) Urinary FSH
 - (a) Decreased
 - (b) Absent
- (11) 17 ketosteroids—low for age

XV COMPLICATIONS SEQUELAE AND ASSOCIATED DISEASES

A FROM INTRACRANIAL PRESSURE

- 1 Visual field defects
 - a Variable
 - b Blindness
- 2 Headache
- 3 Mental aberrations
- 4 Coma
- 5 Epilepsy

B FROM HORMONAL DEFICIENCIES

- 1 Stopped epiphyses
- 2 Unerupted teeth
- 3 Lethargy
- 4 Somnolence
- 5 Diabetes insipidus occasionally^{1 2 3 4 5 6 7}
- 6 Constipation

C RECURRENCE OF TUMOR—This depends on type

- 1 Craniopharyngioma may do so
- 2 Malignant growths often will (see Fig 23)

XVI TREATMENT

A HORMONAL

- 1 Thyroid (desiccated USP)^{6 10 34 35}
 - a Dosage
 - (1) Oral 1 to 2 gr daily
 - (2) Use with caution
 - b Results—may produce unexpected progress in some cases (see Fig 40 Protocol 3 IV Chart 16)
- 2 Chorionic gonadotropin (for males)^{1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100} (see Fig 30, Charts 14 and 15)
 - a Indication—patients who are 12 years of age or more
 - b Dosage intramuscular — 1 000 to 5 000 r.u. weekly
 - c Results
 - (1) Effect on growth is possible

- 7 Somnolence
- 8 Lethargy
- 9 Weakness
- 10 Mental effects
 - a Aberrations
 - b Stupor
 - c Irritability
 - d Psychosis
- 11 Speech difficulties
- 12 Neurologic changes
- 13 Convulsive seizures
- B GROWTH RATE IS RETARDED
- C SECONDARY SEX DEVELOPMENT IS DELAYED
- D GASTRO INTESTINAL
 - 1 Anorexia may be severe at times
 - 2 Polydipsia (diabetes insipidus)
 - 3 Vomiting, may be projectile
 - 4 Constipation
- E GENITO URINARY—Polyuria (diabetes insipidus) (see Fig 34)
- F MISCELLANEOUS
 - 1 Cold sensitivity
 - 2 Pallor
 - 3 Fatigability

XIII DIAGNOSIS

- A RETARDATION OF
 - 1 Growth rate (see Fig 32)
 - 2 Height age
 - 3 Bone age
 - 4 Sexual development
- B LABORATORY DATA
 - 1 Relative lymphocytosis of childhood persists⁴⁰
 - 2 Plasma cholesterol may be increased
 - 3 Serum inorganic phosphorus below 4.5 mg % at any age depending on rate of growth
 - 4 Sugar tolerance usually increased
 - 5 17 ketosteroids are^{27 34 40}
 - a Absent
 - b Very low

XIV DIFFERENTIAL DIAGNOSIS

- A DWARFISM—Eliminate other forms of dwarfism—see 92 V, 93 95
- B HYPOGENITALISM (up to 14 or 15 years of age, during usual pubescent and adolescent periods⁴⁹) (see 1 VI)

1 Definition

a Hypogenitalism in the male ■ used herein indicates a disproportionate genitalia in relation to height age of the individual

b In the female this appraisal is not easy

2 Comment

a It is often difficult to differentiate clinically the various types of hypogenitalism

b When special facilities for study are not available, observations for a year or so may settle the diagnosis

c The following outline should serve to evaluate the significance of hypogenitalism

3 Types

■ Pseudohypogenitalism (male)

(1) Genitalia submerged, due to excess obesity during or before pubescence—normal outcome eventually

(2) Normal range for the following

(a) Height age (often increased)

(b) Bone age

(c) Growth rate

(d) Breast development, enlargement is not uncommon

(e) Testicular size

(f) Urinary FSH

(g) 17 ketosteroids

b Delayed puberty, male and female and hypogenitalism

(1) Transient disorder with or without obesity

(2) Normal range for the following

(a) Height age

(b) Bone age

(c) Growth rate

(d) Breast development

{1} Male—enlargement is common

{2} Female—delayed

(e) 17 ketosteroids

(3) Menarche—delayed

(4) Testes and penis—pubescent size

(5) Urinary FSH

(a) Normal

(b) Increased

c True primary hypogenitalism due to testicular or ovarian disease

(1) Etiology—see 48 IX 65 IX

(b) Growth stimulus may not be maintained

c Adrenocorticotropin and testosterone for males (see above)

9 Cortisone—see 5 VII B 5

B INTRACRANIAL SURGERY^{19 1 40 40}

1 Indications for operation

■ Intracranial pressure with or without localization of tumor if the following are present

(1) Headache, severe

(2) Visual damage

(3) Optic edema

b Large tumors not believed to be radiosensitive

2 Hormonal changes alone are not sufficient criteria for immediate surgery

3 Unnecessary risks should not be taken in any case

4 Air studies

a All cases where tumor is suspected to identify its

(1) Location

(2) Type

b Since chromophobe tumors are rare under the age of 15 it is advisable to establish nature of tumor before considering roentgen therapy. craniopharyngiomas are not very radiosensitive

5 Procedure—see 13 VII A

6 Results—see 12 IV

C ROENTGEN¹⁹

1 Indications

a Chromophobe tumor

b Prophylaxis against return of chromophobe or malignant tumor after operation

2 Procedure—see 13 IX A

3 Results depend on (see Fig 34)

a Radiosensitivity

b Degree of malignancy

XVII PROGNOSIS

A HEIGHT

1 Amount lost during retardation of growth may not be regained

2 Maximum to be hoped for is a normal rate of growth by

a Removal of tumor

b Medical treatment

3 Resumption of growth may take place spontaneously at any age (see Chart 13)

B SEXUAL DEVELOPMENT

1 This does not follow

a Surgery

b Roentgen radiation

2 Spontaneous recovery is possible (see Protocol 3 IV)^{19 40}

3 Pregnancy and newborn may be normal^{11 41 42 43}

4 Hormonal therapy

a Testosterone is helpful in males but spermatogenesis is unlikely

b Estrogens are useful in females

c Chorionic gonadotropin alone or with pituitary gonadotropins may be tried especially in males

XVIII CAUSES OF DEATH

A COMPLICATIONS^{19 40 41}

1 Tumor

2 Postoperative

B PNEUMONIA^{20 71}

C CACHEXIA (see Figs 43 and 44)

D TUBERCULOSIS^{11 43 47}

PREPUBERAL HYPOPITUITARISM

Family history Negative

Past medical Negative

Chief complaint Dizziness of 5 weeks duration

History of present illness Patient had dizzy spells noises in her head which were similar to buzzing sounds and diplopia No history of head injury impairment of speech, or loss of taste and smell Headaches not localized

PROTOCOL I FIG 29 CHART 13

Physical examination Age 14 years Female Weight 72½ lbs Height 54 in BP 102/70

A well proportioned dwarfed child without sexual development Axillary and pubic hair absent Visual fields bitemporal hemianopsia with marked restriction Visual acuity right 20/70 left 20/50 Heart and lungs normal Neurologic examination normal

Laboratory data Urine normal RBC 4 000 000 Hgb 75% WBC 9,600 Differential

- (2) Genital development
 - (3) Other secondary sex characteristics progress
 - (4) Fairly well tolerated and may be continued intermittently
- 3 Testosterone (for males)⁸⁹
- a Indications
 - (1) Promotion of
 - (a) Growth
 - (b) Muscular development
 - (2) To improve anemia
 - b Dosage
 - (1) Oral or buccal—methyltestosterone 20 to 30 mg daily
 - (2) Intramuscular—testosterone propionate, 50 to 70 mg weekly
 - (3) Pellets—testosterone, 150 mg average, implantation every 3 to 5 months
 - c Comment
 - (1) Before the age of 12 testosterone can be used without fear of premature epiphyseal closure
 - (2) Trial of chorionic gonadotropin for 2 or 3 months may be attempted before testosterone
 - (3) 'Lost growth' cannot be recovered
 - (a) Individual remains subnormal in stature
 - (b) One report of dwarf becoming giant⁶¹
 - d Result—growth spurt may not be maintained (see Figs 30 32 34 and 36)
- 4 Estrogens (for females)
- a Indications—to
 - (1) Develop secondary sex characteristics
 - (2) Stimulate growth (doubtful)
 - (3) Establish menstrual flow
 - b Dosage oral
 - (1) Stilbestrol—0.3 to 1 mg daily (if tolerated)
 - (2) Estrone sulfate—0.3 to 1.2 mg daily
 - (3) Other estrogens in comparative dosage progesterone may be used in conjunction with estrogens (see 65 XVI II E)
 - Results
 - (1) Periodic flowing if medication is
- (a) Continued until vaginal bleeding occurs
 - (b) Stopped when flow is present
 - (c) Resumed when menses cease
- (2) Breast development progresses
 - (3) Hair growth is slight some functioning pituitary tissue is needed for adequate response
- 5 Desoxycorticosterone acetate (DOCV)
- a Indication—adrenal insufficiency of clinical significance rarely occurs but is possible (see 40 VIII)⁶⁰
 - b Dosage pellet—75 mg
 - c Results
 - (1) Well being improves
 - (2) Blood pressure rises
 - (3) Tolerance for desiccated thyroid may increase when testosterone is also administered
- 6 Adrenocorticotropin (see 106 III E)
- a Indications
 - (1) Same as for desoxycorticosterone
 - (2) Anorexia
 - b Dosage intramuscular—10 mg daily
 - c Results—should be favorable, based on adult studies
 - d Addition of testosterone is probably advisable in males
- 7 Growth hormone or anterior pituitary extracts have not yielded very satisfactory results to date^{7 3 9 37 38 41 48 73 74 77 84 88}
- 8 Combinations
- a Growth hormone with desiccated thyroid
 - (1) Dosage intramuscular
 - (a) Growth hormone—1 to 3 cc 5 to 7 times a week
 - (b) Chorionic gonadotropin—1 000 to 2 000 units 3 times a week
 - (2) Results—variable
 - b Testosterone and estrogen therapy in the female
 - (1) Indication—greater growth stimulus than with estrogens alone
 - (2) Dosage as above
 - (3) Results
 - (a) Estrogen may offset masculinizing effects

MONTHS

- 18 Growing slowly Testes firm, small olive size Urinary I²⁵S¹²⁵H negative un concentrated 17 ketosteroids 2.08 mg / 24 hrs Bone age 13½ years Thyroid, 2 gr daily to be continued
- 33 Further growth Erections at times Testes larger Plasma cholesterol 136 mg % Urinary I²⁵S¹²⁵H negative 17 ketosteroids 3.0 mg / 24 hrs (880 cc volume)
- 44 Weight 120 lbs Grew 1½ in in past 12 months Testicles larger No sexual hair Methyltestosterone, 10 mg b i d to t i d
- 47 Height 59 in Noted no effect from testosterone, so stopped taking it Chorionic gonadotropin (APL) 1 cc (1 000 units) injections 3 times a week
- 49 Pubic hair and axillary hair appeared while on APL injections
- 54 Gained 19 lbs Grew 1¾ in with APL injections Height 60¾ in Genitalia larger Approximate volume of each testis 13 to 18 cc Bone age 15¼ yrs
- 66 Weight 135 lbs Height 61¼ in No medication for 9 months Penile erec

tions No facial hair Testes same size Serum phosphorus (fasting) 4.8 mg %

- 76 Weight 141 lbs Height 61½ in No medication for 10 months Grew only ¾ in, but bone age at stage when growth rate declines Serum phosphorus 4.7 mg %

Comment Dwarfism of pituitary origin illustrating retardation of growth and sexual development but otherwise a well and active patient Suprasellar cyst suspected but never proved Hypogenitalism was related only to chronologic age, but not to height or somatic age The marked discrepancy between bone and chronologic ages is characteristic of pituitary dwarfism in contrast with simple delayed puberty Continued increment of growth with some response to methyltestosterone and further development with chorionic gonadotropin On cessation of chorionic gonadotropin and testosterone there was less progress Inorganic serum phosphorus levels suggest independent growth hormone activity Although 25 years of age sexual maturity may still occur

PREPUBERAL HYPOPITUITARISM

PROTOCOL III

FIGS 36, 37

CHARTS 14 15

Family history Negative

Past medical Negative

Chief complaint Failure to grow normally about 2 years

History of present illness From 3 to 6 years before admission it became apparent to his parents that the patient was not growing as other children His brother 2 years younger was one head taller Intelligence average junior in high school

Physical examination Age 14 male single Weight 61 lbs Height 49 in Pulse 80 BP 95/70 A small well proportioned boy with physical characteristics of an 8 year old Pubic and axillary hair absent Breasts normal Penis and testes very small

Laboratory data Urine normal Plasma cholesterol 229 mg %

Roentgenographic findings Skull—ella normal definite widening of the coronal and sagittal sutures for his age possible in

creased intracranial pressure Dental age 12 or 13 years Bone age 7 to 8 years

Treatment and progress

YEAR

- 1 Growing very slowly RBC 4 080 000 Hgb 77% WBC 6 150 Differential polymorphonuclears 47% lymphocytes 35% monocytes 6% eosinophils 10.5% basophils 1.5% Plasma cholesterol 316 mg % Skull—sutures lines remain open but are not separated sella normal
- 2 Growing very slowly Thyroid (desiccated USP) ½ gr daily restarted and continued for 1 year
- 5 Thyroid medication stopped
- 7 Growth very slow Absent sexual development and beard Feels perfectly well Blood counts the same Blood sugar 110 mg % (1½ hrs p c) Plasma cholesterol 253 mg % BMR

polymorphonuclears 56% lymphocytes 31%, monocytes 6% eosinophils 2%
Spinal fluid normal

Roentgenographic findings Sella measures 14 mm in A-P and 8 mm in depth lateral area approximately 100 sq mm Posterior clinoids are upright in position and slightly thinned, calcification in midline just above the sella Total area of calcification measures more than 2 cm in diameter Chest normal

Treatment Operation—large suprasellar craniopharyngioma was found and removed

Progress

MONTHS

14 Growth resumed No sexual development Mild diabetes insipidus RBC 4,640,000 Hgb 15.1 Gm WBC 8,000 Differential polymorphonuclears 44%, lymphocytes 46% monocytes 5% eosinophils 5% Plasma cholesterol 124 and 179 mg % Serum phosphorus 4.0 mg % Adrenal water test positive Urinary hormones FSH negative, estrin grade one 17 ketosteroids 2.5 mg/24 hrs

20 Stilbestrol ointment rubbed into axillae and pubis No hair growth

YEARS

3 Anterior pituitarylike hormone 1 cc (1,000 units) 3 times a week for 3

months without effect Stilbestrol, 0.5 mg orally daily

4 Stilbestrol 0.5 mg orally, tid and thyroid 1 gr daily for 18 months Occasional menstrual flow Oreton "M" ointment rubbed into axillae for several months No hair growth

6 Weight 138 lbs Final height 64½ in. Feels perfect Normal intake of water No pubic or axillary hair Breasts enlarged and deeply pigmented Thyroid 1 gr daily

Comment This case illustrates the usual history of a patient with craniopharyngioma namely retarded growth about which nothing was done, and cerebral symptoms for which medical advice was sought Operation was successful with resumption of normal growth rate but no further sexual changes were noted Mild diabetes insipidus developed postoperatively, and disappeared in several years Low 17 ketosteroids were found and a positive water test for adrenal cortical insufficiency In spite of latter, general strength and activity were normal No response to chorionic gonadotropin Stilbestrol caused enlargement of breasts and menstrual bleeding Growth rate apparently slowed down on this medication No growth of pubic or axillary hair with stilbestrol or axillary hair by localunction of testosterone ointment

IRPUBERAL HYPOPITUITARISM—GROWTH AND GONADOTROPIC DEFICIENCY

PROTOCOL II FIG 30

Family history Father 65 in 150 lbs Mother 66 in 103 lbs Sister age 15, 65 in, 101 lbs

Past medical Pneumonia

Chief complaint Failure to grow

History of present illness Underweight since 8 years old but gained slowly for past 2 years At age 15 50 in and 84 lbs Grew 8 in from 11 to 17 years Mental development normal, junior in high school

Physical examination Age 17 male single Weight 90 lbs Height 54 in BP 104/96 Small for his age but well proportioned Short fat arms and legs Small hands and feet Skin smooth Fundi normal Thyroid not palpable Breasts prominent Fat belt around lower portion of abdomen Genitalia proportionate to height age

Laboratory data Urine normal RBC 5,040,000 Hgb 92% WBC 7,450 Differential polymorphonuclears 55% lymphocytes 34%, monocytes 6%, eosinophils 4%, basophils 1% Plasma cholesterol 117 mg %

Roentgenographic findings Skull—posterior clinoids directed posteriorly No other signs of intracranial lesion Dental age 13 to 14 years Bone age 12¼ years

Treatment and progress

MONTHS

10 Thyroid (desiccated USP) 1 gr daily and gradually increased to 2 gr Grew a little No sexual hair Plasma cholesterol 153 mg %

Treatment and progress (see growth chart) MONTHS

- 0 Thyroid (desiccated USP) $\frac{1}{2}$ gr daily because of cholesterol and metabolic rate
- 2 Grew 1/16 in on thyroid medication Appetite improved
- 3 Thyroid dose increased to 1 gr Grew $\frac{1}{2}$ in Two deciduous teeth appeared
- 7 Patient growing No weight gain Bone age 6 years Thyroid 1 gr daily continued haliver oil 1 capsule daily 1 year vitamin B syrup (Meads) 2 teaspoonfuls daily 6 months
- 19 Bone age 10 years Patient was sent to Teloban for injections Unfortunately he already began to show pubic hair so that the pituitary preparation had no relationship to the onset of puberty (between 17 and 18 years of age) No growth spurt noted as result of injections
- 26 Bone age 12 to 14 years Thyroid 2 gr daily
- 34 Three gr of thyroid for 2 months then no further treatment
- 36 Bone age 15 $\frac{3}{4}$ years
- 55 Patient was not seen since the thirty-sixth month of treatment Plasma cholesterol (note on chart) which had been elevated at the onset and had de-

creased with thyroid administration, was lower than while taking it 2 years previously Radial epiphyses closed

- 57 Measurement from the umbilicus to floor was 28 $\frac{1}{2}$ in Weight 70 lbs Proportionate development for height age Facial lanugo was present Testes normal for patient's size Prostate was small RBC 4 890,000 Hgb 99% Sperm count 104 000,000/cc, 80% motile majority were normal few with large round heads short thick necks and some miniature forms EKG normal 17 ketosteroids 33 mg/24 hrs (volume 200 cc) Chest and skull normal Thyroid (desiccated, USP) 1 gr started for 2 weeks then increased to 2 gr daily
- 63 Axillary hair present and facial hair had increased Voice changing Normal sexual drive Height remained 50 in Good health 17 ketosteroids 10 mg/24 hrs (volume 650 cc) Urinary FSH negative (unconcentrated)

Comment Dwarfism of pituitary origin affecting only growth and possibly thyrotropic hormone Desiccated thyroid appeared to stimulate growth and normal sexual development between 17 and 18 years Final height 50 in

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- minus 18% Skull sutures remain open Dental age 13 years Epiphyseal status (bone age) 13 years approximately Tetosterone in glycolalcohol, 6 mg daily sublingually Thyroid 2 gr daily
- 8 Slight increase in pubic hair and a few penile erections Plasma cholesterol, 223 306 and 250 mg % Urinary FSH negative (unconcentrated) 17 ketosteroids 9.1 mg/24 hrs Bone age 15 years Methyltestosterone 20 mg daily for 2 months Seven testosterone pellets were implanted 3 on one occasion, 4 on the next
 - 9 Slight moustache more hair around the pubic area Few erections Voice lower Further secondary sex changes Testes not enlarging Plasma cholesterol 133, 178 and 254 mg % Urinary FSH positive 17 ketosteroids, 6.8 mg/24 hrs (volume 520 cc) Bone age 16½ years Desiccated thyroid used intermittently to determine its effect on growth Testosterone pellets were inserted 4 times total of 18
 - 10 Fewer erections than before Voice unchanged No growth on thyroid and/or testosterone Plasma cholesterol 217 and 248 mg % Serum phosphorus 3.6 mg % Urinary hormones FSH negative, estrin negative, 17 ketosteroids 5.6 mg/24 hrs (volume 1,500 cc) Thyroid was taken irregularly Testosterone pellets, total of 8 during 9 months More erections Testicles no larger Semen volume 5 cc, sperm have no heads and are inactive Sella measures 68 sq mm Bone age 17 years Four testosterone pellets
 - 12 General condition about the same No complaints Above average intelligence Testicular volume about 5 cc each Chorionic gonadotropin, 3 000 to 5 000 units per week, for 7 months without testosterone Erections maintained Adrenal water test negative
- Comment* Pituitary dwarfism which responded to testosterone therapy Although patient always felt well, there was apparently some secondary thyroid deficiency Adrenal water test negative Urinary FSH negative twice and positive once 17 ketosteroids from 5 to 9 mg/24 hrs Increased erections and nocturnal emissions on chorionic gonadotropin but little or no increase in testicular size, showing that Leydig cells reacted but tubules did not and no spermatozoa were seen in ejaculate The cause of tubular failure might be assigned to long absence of stimulation independent disease of tubules or too much testosterone

PITUITARY DWARFISM

Family history Grandmother and mother each about 4 ft 10 in in height Father was 5 ft 7 in Two brothers were of normal height

Past medical At birth weighed 7 to 8 lbs therefore normal in size although no measurement of length recorded He seemed to develop normally until about 4 yrs of age when he stopped growing At 8 yrs of age he was a patient at the Peter Bent Brigham Hospital Weight 28 lbs Height 35½ in Physical examination was summarized there as follows Proportional infantile boy, skin dry pale a few more wrinkles on the face than usual and little subcutaneous fat Mentality advanced Skull negative Delayed dental development Diagnosis Summonds disease Bone age 2.9 years

PROTOCOL IV FIGS 40-42 CHART 16

Chief complaint Failure to grow
History of present illness Patient has been normal except for his stature He has grown about 2 in a year since age of 10
Physical examination Age 15 male, single Weight 41 lbs Height 40¼ in Span 38½ in Pulse 76 BP 108/70 Alert mentally (in second year of high school) Proportionate infantile boy Hair fine normal amounts Genitalia fat pad over pubis penis and testes undersized
Laboratory data Urine normal RBC 4 300, 000 Hgb 78% WBC 10 800 NPN 24 mg % Plasma cholesterol 280 mg % BMR minus 18%
Röntgenographic findings Skull normal with very few convolitional markings Epiphyseal status (bone age) 4½ years Chest normal

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FIG. 29 PANHYPOPITUITARISM CAUSED BY A SUPRASELLAR CYST (See Protocol 31 Chart 13) Age 14 Height 58 in Height age 12 to 13 years Span 57½ in Bone age 12½ years BMR plus 7%. Patient shows retarded growth and sexual development due to craniopharyngioma. These abnormalities were not considered important by her parents until she complained of double vision and dizziness associated with head noises. Mentally precocious. Resumption of normal rate of growth after craniotomy but no sexual development or regrowth of body lanugo. Mild diabetes in ipidus since operation.

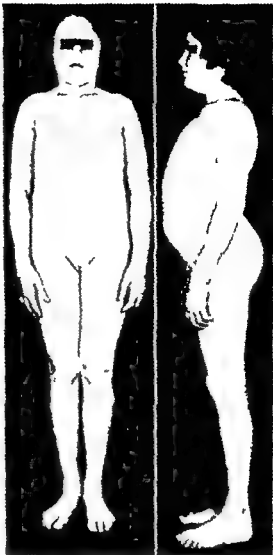


CHART 13 PANHYPOPITUITARISM (See Fig 29) Growth chart before and after operation for craniopharyngioma. Note that growth has continued into the nineteenth year having been retarded since the age of 8 and accelerated after operation. (1) Stilbestrol injection in left axilla (0.5 mg daily) was without effect. Treatment with chorionic hormone and pregnant mare serum was unsuccessful. (2) Stilbestrol (0.5 to 1.5 mg daily) administration beginning at the age of 19 produced menstruation and slight enlargement of breasts without pubic or axillary hair growth. Linear growth slowed down with this treatment. Injections of testosterone in axillae failed to cause hair growth there.

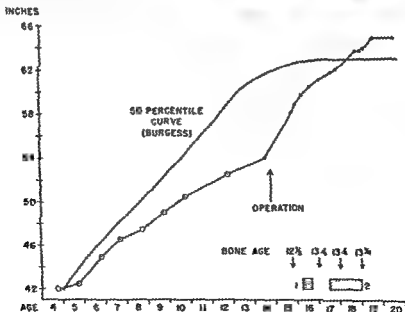




FIG 27 FROHLICH'S SYNDROME Illustrating that retardation of growth and sexual development and not obesity are the important physical findings in this disorder Age 14 estimated height 46 to 48 in Height age 7 to 8 years Although obesity is reported to have occurred in this patient at a later date it is now considered to have resulted from hypothalamic injury rather than anterior pituitary hypofunction The patient suffered from headaches and visual changes due to a suprasellar cyst (Frohlich A Ein Fall von Tumor der Hypophysis cerebri ohne Akromegalie Wien klin Rundschau 15 883)

FIG 28 LORAIN LEVI TYPE OF INFANTILISM This disorder is the same as Frohlich's syndrome The two sisters shown here were 15½ and 20 years of age In one an enlarged sella was demonstrated along with visual changes no such abnormality was found in the other Both were dwarfed (51 and 52 in height age 9 to 10 years) and had no sexual development (Faneau de la Cour a student working with Lorain first published a description of infantilism associated with pulmonary tuberculosis hence the reason for the term Lorain Levi Gynecomastia as well as eunuchoidism without dwarfism was also described in the same article Faneau de la Cour Du feminisme et de l'infantilisme chez les tuberculeux Jan 1871 Faculte de Medecine) (Reproduction of illustrations from original article Levi E Contributions a l'etude de l'infantilisme du type Lorain Nouv icon de la Salpet 21 297)

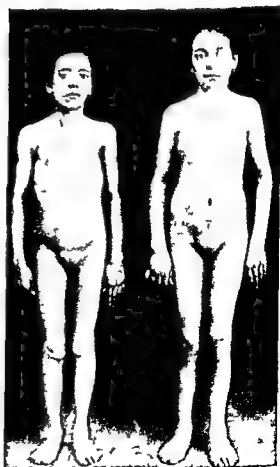




FIG 32 HYPOPITUITARISM WITHOUT GROWTH RETARDATION (See Fig 33) Complaints pallor and weakness Age 19 Height 67 $\frac{1}{4}$ in taller than parents and 6 siblings Span 68 in Bone age 16 years No axillary pubic or body hair Testes approximate volume 55 cc (average for 14 year old) RBC 3 200 000 to 4 600 000 Hgb 72 to 83% and 83% after testosterone therapy Differential polymorphonuclears 55% lymphocytes 37% monocytes 3% eosinophils 2% and basophils 2% Plasma cholesterol 230 mg % Adrenal water test positive 1/ ketosteroids 3.8 mg/24 hrs Sella enlarged and unusual in shape Visual fields normal No headaches Surgery and air studies not indicated No improvement on 20 units of gonadogen 3 times a week for 6 months other than a few erections for several months Testosterone by pellets or sublingually caused improvement in well being strength and endurance Pubic hair developed but fell out when treatment was omitted Height at 22 was 69 in span 72 in Bandage is over site of pellet implantation

FIG 33 HYPOPITUITARISM WITHOUT GROWTH RETARDATION (See Fig 32) Sella enlarged measuring 10 x 15 mm or 133 sq mm The cause of sellar enlargement in this case is obscure it does not appear like the usual intrasellar tumor and there is no increase in size over a 3 year period The patient differs from an individual with hypopituitarism from suprasellar cyst because there is no growth retardation A mixed pituitary tumor might produce this clinical syndrome



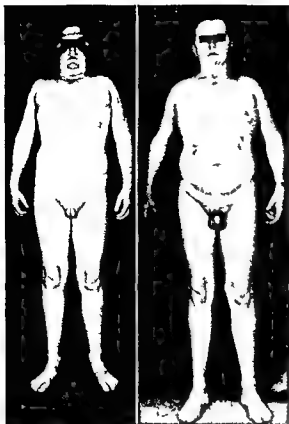


FIG 30 PITUITARY DWARF (See Protocol 3 II) (*Left*) Age 17 Height 54 in Height age 10½ years Bone age 11 years Gradual growth for 3 years not accelerated by treatment with desiccated thyroid Genitalia not disproportionately small for height age Testicular volume estimated 4 cc (*Right*) Height 60¼ in (5 years later) Testicular volume 8.5 cc after 11 months of methyltestosterone (10 to 20 mg daily) No apparent increase in growth rate On chorionic hormone (1000 units 3 times a week) for the greater part of 9 months patient grew 1¾ in an increased growth rate Testicular volume estimated 13 in 18 cc Note condition of genitalia

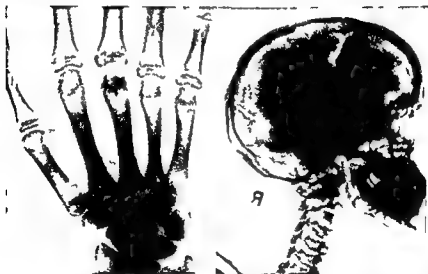


FIG 31 CRANIOPHARYNGIOMA AND PANHYPOPITUITARISM (*Right*) Skull in an individual 25 years of age Note the large suprasellar cyst with calcification the underdevelopment of the sinuses the rather thin cranial bones and the open sutures The result of craniotomy (by Dr Harvey Cushing) at the age of 16 is seen which probably permitted further growth but absence of secondary sex characteristics remained Weight 97 lbs RBC 4 600 000 Hgb 92% Plasma cholesterol 164 mg % Serum sodium 125.5 mEq/l Serum potassium 17.3 mg % Plasma chlorides 503 mg % Glucose tolerance test ½ hr 60 mg % 1 hr 100 mg % BMR minus 40% Bone age 15 years (*Left*) Hand of patient demonstrating open epiphyses which are slow but continual growth until age of 25 when he attained a height of 67½ in

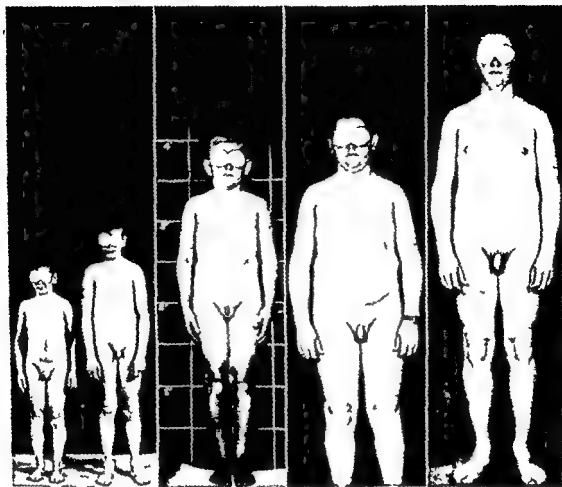


FIG 36 HYPOPITUITARISM (See Protocol 3 III Fig 37 Charts 14 and 15) (Extreme left) Pituitary dwarfism predominantly growth sex and thyroid deficiencies without evidence of pituitary tumor or craniopharyngioma but with a small sella turcica Patient (left) age 14 and brother age 10 No complaints other than failure to grow for the previous 8 years Note amount and contour of pubic fat as compared with brother Mentally alert and normal intelligence Height 49 in Height age 8 years Bone age 7 years Weight 67 lbs RBC 4 000 000 Hgb 17% Plasma cholesterol 229 to 316 mg % BMR minus 18% (Left of center) Close up of subject at left (Right of center) Patient at age 21 Weight 132 lbs Height 59½ in Bone age 13 years RBC 4.1 million Hgb 76% Blood sugar 110 mg % (1½ hrs) Plasma cholesterol 253 mg % BMR minus 18% Treatment failed to produce any marked change in growth (Extreme right) End result of therapy demonstrated No acceleration of growth produced although epiphyseal closure took place Final height 63½ in Normal libido and ejaculation but aspermatia Testes approximate volume 5.5 cc Patient takes methyltestosterone and desiccated thyroid Adrenal water test negative

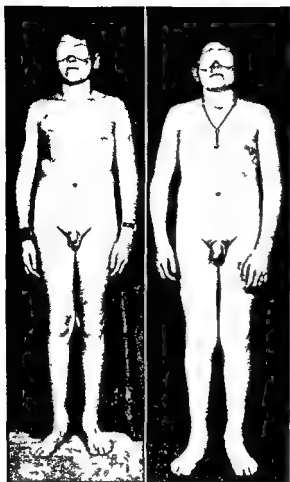


FIG 34 PINEALOMA SIMULATING CRANIO-PHARYNGIOMA (See Fig 35) (*Left*) Photograph of patient shortly after operation. The tumor was malignant and was considered to be a pinealoma (Dr Louise Eisenhardt). Intensive irradiation after operation consisted of 4 000 r total to each of 3 portals. Patients complained of headache and had a bitemporal hemianopsia before operation. A mild diabetes insipidus was also present. He was 12 years of age and measured 56 1/2 in (normal for age). Bone age normal (12 years). (*Right*) After testosterone therapy. From time of operation age 12 little growth occurred. One year after operation when thyroid (desiccated USP) 2 gr was given a drop in weight followed but there was a consistent increase in growth. This apparently ceased when thyroid was discontinued and little effect was noted when it was resumed in a dose of 1 gr daily. There probably was a further stimulation of growth and weight on gonadotropic and chorionic hormones which continued after giving methyltestosterone and testosterone pellets. Testes increased approximately from 3 1/4 to 1 1/4 in long (volume 2 to 4.5 cc approximately).

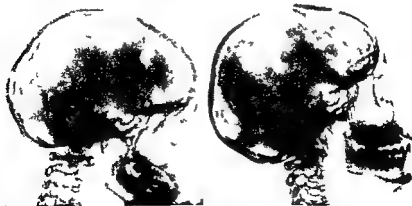


FIG 35 PINEALOMA SIMULATING CRANIO-PHARYNGIOMA (See Fig 34) Roentgenograms after operation (*Left*) 11 months (*Right*) 18 months (essentially the same as before). Note recalcification of the posterior clinoids and smaller size of the sella a finding often seen after successful radiation therapy.

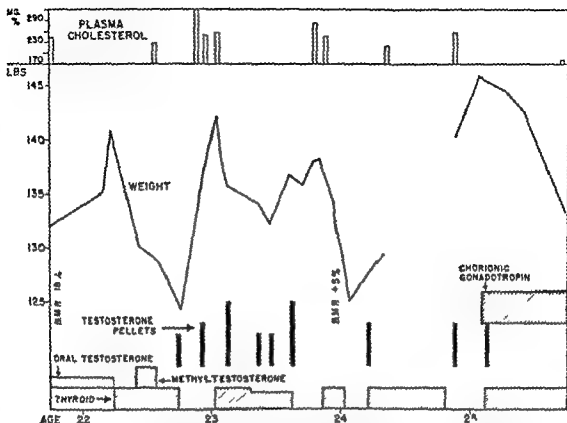


CHART 15 PITUITARY DWARFISM (See Protocol 3 III Figs 36 37 Chart 14) Effect of testosterone and thyroid (desiccated USP) on weight. Average growth rate before treatment was $1\frac{1}{2}$ in/year after treatment each year first $1\frac{1}{2}$ in second $1\frac{1}{4}$ in third $\frac{3}{8}$ in fourth no growth. Epiphyseal closure took place during last 2 years which accounted for slow ing down in growth. No growth stimulation was accomplished with testosterone with or without thyroid (desiccated USP). The weight gain with testosterone is well shown and its tendency to prevent weight loss when thyroid (desiccated USP) is given. Chorionic hormone caused some increase in testicular size and also maintained the frequency of erections. However no spermatogenesis was evident after 6 months of chorionic hormonal therapy. The BMR was minus 18% without thyroid (desiccated USP) and the plasma cholesterol varied with 233 to 308 mg %. With thyroid (desiccated USP) the BMR was plus 5% and the plasma cholesterol was from 172 to 217 mg %.

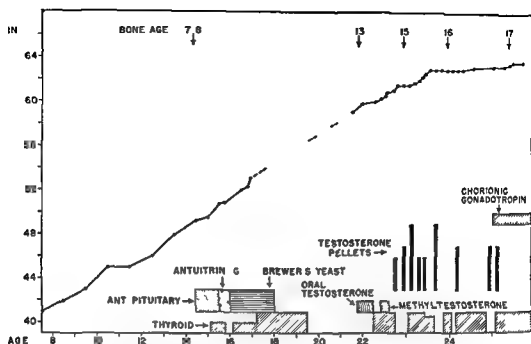


CHART 14 PITUITARY DWARFISM—GROWTH CHART (See Protocol 3 III Figs 36 37 Chart 15) No effect on rate of growth with various forms of treatment. At 8 years of age patient was underheight (below 1 percentile curve by Burgess). Treatment with anterior pituitary extract and thyroid (desiccated USP) ineffective. With growth hormone there appeared to be a spurt in growth and later with desiccated thyroid. This chart demonstrates the danger of making conclusions regarding the effects of any therapy over short periods of time. The dotted line represents a time span where no observations are made. See Chart 15 for effect of thyroid (desiccated USP) and testosterone on weight in this case.

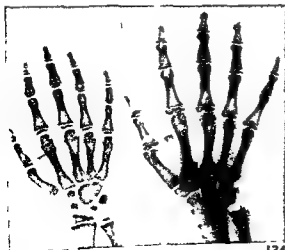


FIG 37 BONE MATURATION IN PITUITARY DWARFISM (See Protocol 3 III Fig 36 Charts 14 and 15) Bone age on admission and 7 years later. (Left) Age 14 bone age 7 to 8 years. (Right) Age 21 bone age 13 years.

FIG 40 PITUITARY DWARFISM (See Protocol 3 IV Figs 41-42 Chart 16.) Apparent response to treatment with desiccated thyroid. Epiphyses closed at 21 years. Normal sexual development with normal spermatogenesis. Final height 50 in. Height age $3\frac{1}{2}$ years.



FIG 41 PITUITARY DWARFISM SELLA ROENTGENOGRAMS (See Protocol 3 IV Figs 40-42 Chart 16.) (Left) Age 8. Dental age on roentgenograms was not retarded. Sella measured 6×4 mm. and the lateral contour area 33.5 sq. mm. which is small for chronologic age as well as for height age of $4\frac{1}{2}$ years. (Right) Age 21. Dental age on roentgenograms was not retarded. The change in the sella size was slight and is still small for his height age. Note shape of skull which is unlike that of cretins. Poor development of sinuses. Sutures are open.



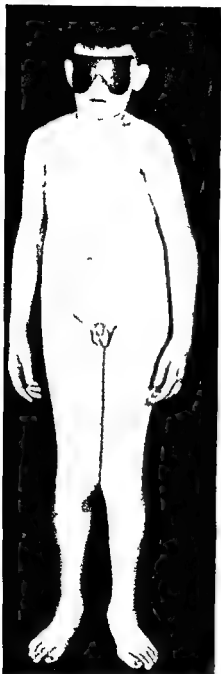


FIG 38 HYPOPITUITARISM (?)

Condition associated with central nervous system disease possibly due to birth injury. Mother had toxemia of pregnancy; child was delivered 2 months prematurely by internal podalic version and breech. Birth weight 4 lbs 9 oz. Mentally alert. Bilateral flexion contractures of both knees with muscular atrophy. Age 1/

Height 62 in. Height age 14 to 15 years. Bone age 14 years. BP 90/10. RBC 3,400,000. Hgb 11.5 Gm. Differential normal. Plasma cholesterol 188 mg %. BMR minus 20 %. Urinary FSH questionable weak positive. 17 ketosteroids 3.7 mg/24 hrs. Treated with methyltestosterone (40 mg daily) with resulting weight gain and genital development. Final outcome unknown.

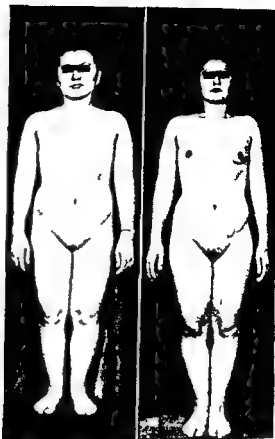


FIG 39 HYPOPITUITARY DWARF (Left) Age 17. Bone age 10 years. Height age 10 years (53 in). Serum phosphorus 3.8 mg %. Urinary FSH negative. Only complaint failure to menstruate. Unresponsive to chorionic hormone and pregnant mare serum. (Right) Age 21. Bone age 13½ years after 6 months of stilbestrol therapy (0.5 to 1 mg daily). Height age 11 years (55½ in). Periodic menstrual flow, enlargement of breasts and some growth of pubic and axillary hair. (Patient always had some hair on arms and legs). Urinary pregnandiol negative preceding menstrual flow. Compare with Figure 29 in which breast development and menstrual flow occurred without hair growth. At age 23 spontaneous menstruation occurred regularly without medication for 6 months.

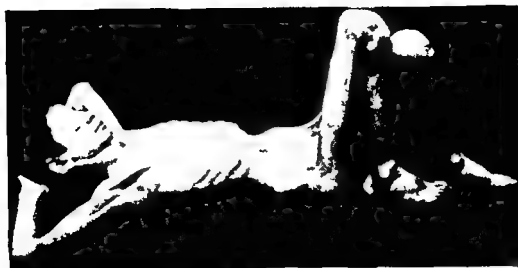


FIG 43 PITUITARY DWARFISM (See Fig 44) Pituitary cachexia at time of initial operation for craniopharyngioma age 12 (Dr Harvey Cushing)



FIG 44 PITUITARY DWARFISM (See Fig 43) Age 39 Height 54 in Patient in coma Rectal temperature 92° F Blood sugar 40 to 50 mg % Note plentiful hair of head and eyebrows Genital atrophy Death occurred with gradual decline in respiration (very shallow) and blood pressure as if passing from hibernation to complete cessation of life Cessation of growth and head aches at 12 years of age relieved by operation Vision in right eye not restored Extreme emaciation at that time Second operation 15 years later for restoration of vision in left eye which was almost completely lost Cystic mass found involving left optic nerve and retrochiasmal region Sight not restored Developed mental confusion and drowsiness Readmitted to hospital 1 year later in coma and died without further attempts to remove cyst or fluid Epiphyses still open Roentgenograms of skull showed calcification 4 cm in diameter in midline and behind the sella with loss of posterior clinoids

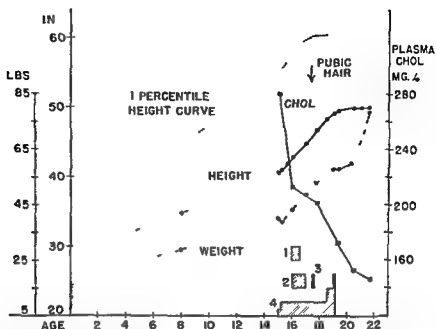


CHART 16 GROWTH CHART IN PITUITARY DWARFISM (See Protocol 3 IV Figs 40-42)
 The slow and verified rate of growth until the age of 15 is followed by an accelerated rate on administration of thyroid (desiccated USP). Note that growth slowed down when thyroid was discontinued but this was due to closing epiphyses. Thyroid was not stopped earlier because of his parents' desire not to interfere with the apparent effect of treatment. It is to be noted that the plasma cholesterol did not rise after omitting the medication. However, the patient continues to take 1 gr. of thyroid (desiccated USP) daily because he feels better and is less constipated. Without the drug the patient did not develop evidence of thyroid deficiency. Figure 40 shows him at that time. All the hollow and black circles represent recorded measurements. Plasma cholesterol is illustrated by black squares.

Key to therapy symbols in lower right section of chart: (1) Vitamin H complex 1 teaspoonful 3 times a day (2) Halver oil capsule 3 times a day (3) Praeloban 100 mg twice a week (4) Thyroid (desiccated USP) $\frac{1}{2}$ to 3 gr daily

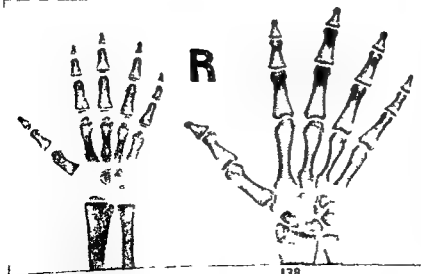


FIG 42 PITUITARY DWARFISM HAND AND WRIST ROENTGENOGRAMS (See Protocol 3 IV Figs 40-41 Chart 16) (Left) Age 8 years Height 40 $\frac{3}{4}$ in Height age 4 $\frac{1}{2}$ years Bone age 2 $\frac{9}{10}$ years (Right) Age 21 Height 50 in Height age 8 years Bone age 17 years

E INTRODUCTION

- 1 General
 - a Texture Cool, nails brittle⁶
Normal smooth rarely may be caly wrinkling if pituitary myxedema is present
 - b Temperature Subnormal
 - c Moisture Subnormal
 - d Eruptions None characteristic
 - e Pigmentation Light brown or yellowish none on mucous membranes no black freckles
 - f Color Often marked pallor
- 2 Hair
 - a Head Fine thin but abundant, may fall out but only after body hair is gone
 - b Facial Usually scant in males
 - c Axillary Scant or absent, if removed may not regrow at normal rate
 - d Pubic Decreased or absent
 - e Body Decreased or absent including lanugo

F HEAD

- 1 Shape and size Normal
- 2 Facial expression Normal possibly dull
- 3 Eyes
 - a General Normal lids may be swollen nystagmus sometimes
 - b Fundi Occasionally papilledema frequently optic atrophy of one or both eyes
 - c Visual
 - (1) Fields Normal but more often restricted bitemporal hemianopsia homonymous quadrantal achromatopsia with tumor
 - (2) Acuity Normal or decreased
- 4 Ears and nose Normal
- 5 Mouth and throat
 - a General Normal
 - b Teeth Normal
 - c Larynx (voice) Normal or high pitched

G NECK

- 1 General Normal
- 2 Thyroid Normal

H CHEST

Normal

I HEART AND PERIPHERAL VESSELS

- 1 Heart Normal or diminished size
- 2 Rate and rhythm Normal or slow
- 3 Blood pressure Normal or low unless onset after previous hypertension^{3 7}
- 4 Peripheral arteries and veins Normal or poor tension
- 5 Vasomotor Subnormal response to stimulation

J BREASTS

- 1 Male Normal
- 2 Female Normal or various degrees of atrophy

K ABDOMEN

- 1 Liver Normal
- 2 Spleen Normal rarely enlarged¹⁰

SECTION 4

POSTPUBERAL HYPOPITUITARISM

I DEFINITION

A postpuberal condition resulting from diminished secretions of the anterior pituitary gland generally affecting all hormones in variable degrees but especially the gonadotropic, thyrotropic and adrenocorticotrophic hormones. Clinically, the condition is best exemplified by the hypopituitarism associated with chromophobe or suprasellar cysts or tumors. Hypothalamic involvement may contribute to the frequent difference between hypopituitarism caused by tumor and that found in Simmonds disease. Some writers make no differentiation, except for etiology and occurrence in females. It must be admitted that the two may be indistinguishable. All cases of chromophobe tumor do not have demonstrable hormonal deficiencies.

II APPEARANCE

Normal or may retain youthful countenance. Skin smooth and pale. Males take on a female habitus (see Figs 45-49).

III AGE

Any in postpuberal period³

IV SEX

Equal distribution

V MENTAL DEVIATIONS

A INTELLIGENCE

Normal variation

B RESPONSIVENESS

Normal or slow

C OTHER ABNORMALITIES

Normal or lapses of memory, somnolence—"pituitary hibernation," psychosis occasionally, rarely insomnia³

VI PHYSICAL STATUS

A NUTRITION

Good in most cases

1 Weight

Variable

2 Fat distribution

Reversion of male type to feminine distribution may have rapid accumulation around abdomen and hips

B HEIGHT

Normal unless onset before epiphyseal closure, then retarded

C EXTREMITIES

1 Upper

Normal

a Hands

May be pudgy and somewhat puffy

b Fingers

Tapering fingers unimportant in diagnosis except in contrast with advanced cretinism

c Span

Normal

2 Lower

Normal

a Feet

Normal variation swelling occasionally

b Toes

Normal

D SPINE

Normal

- a Normal
- b Small (may have increased colloid)
1-13
- 3 Parathyroids—normal
- 4 Adrenals
 - a Normal
 - b Hypoplasia¹ 13
 - c Atrophy²
- 5 Testes¹ 1-13
 - a Normal
 - b Atrophy
- 6 Pancreas
 - a Normal
 - b Atrophy
- 7 Thymus
 - a Small
 - b Enlarged
- 8 Cerebral lesions¹
 - a Infundibular tumor
 - b Glioma
 - c Endothelioma
 - d Hydrocephalus
- 9 Liver
 - a Normal
 - b Fatty changes
- 10 Prostate¹¹
 - a Normal
 - b Atrophy
- II MICROSCOPIC
 - 1 Pituitary—variety of lesions—see 2 IV
B 12 a e
 - 2 Testes (see Fig 50)¹³
 - a Leydig cells—absent
 - b Seminiferous tubules
 - (1) Normal
 - (2) Hypoplasia
 - c Sertoli cells—normal
 - d Spermatogenesis
 - (1) Decreased
 - (2) Absent

XI PATHOLOGIC PHYSIOLOGY

—see 5 VI

XII SYMPTOMATOLOGY

- A IF TUMOR AND/OR INTRACRANIAL PRESSURE—see 13 VI 5 6 8 9
- B GASTRO-INTESTINAL
 - 1 Polydipsia only if neurohypophysis involved
 - 2 Weight rapidly
 - a Increased
 - b Lost
 - 3 Anorexia occasionally

- 4 Constipation
- 5 Hypoglycemic reactions with fasting

C GENITO URINARY

- 1 Polyuria (diabetes insipidus)
- 2 Impotence
- 3 Libido lost
- 4 Amenorrhea
- 5 Sterility

D MISCELLANEOUS

- 1 Cold sensitivity
- 2 Pallor
- 3 Fatigability

XIII DIAGNOSIS

A SYMPTOMATOLOGY

- 1 Hormonal
 - a Amenorrhea (with decreased or absent FSH)
 - b Libido lost in both sexes
 - c Fatigability
 - d Weakness
- 2 When tumor is present
 - a Headache
 - b Visual damages
 - c Somnolence

B SIGNS

- 1 Visual field changes only with tumor
- 2 Optic atrophy with certain growths
- 3 Skin—smooth
- 4 Pallor—often
- 5 Secondary sex characteristics regress in varying degrees

C LABORATORY DATA

- 1 Cholesterol (plasma)—normal (rarely over 230 mg %)
- 2 Basal metabolism rate low (minus 20% to minus 40%)
- 3 Water test—positive
- 4 17 Ketosteroids—very low (0.4 mg /24 hrs)
- 5 Sella turcica—usually enlarged

XIV DIFFERENTIAL DIAGNOSIS

- A FATIGUE STATES (i.e., chronic nervous exhaustion or anemia)
 - 1 The following are usually normal
 - a Menstrual cycle
 - b Libido sexualis
 - c Secondary sex characteristics (male and female)
 - d Visual fields
 - e 17 Ketosteroids
 - f Sella turcica

3	Hernia	None
4	Tumor	None
L GENITALIA		
1	Male	
a	Penis	Normal or slight regression in size
b	Testes	Variable degree of atrophy ¹⁴
c	Prostate	Atrophic ¹³
2	Female	
a	External	Atrophic
b	Internal	Atrophic
M NEUROMUSCULAR		
1	Muscles	Normal or weakened
2	Gait	Normal or unsteady
3	Body movements	Normal or slow
4	Tremor	None
5	Paresthesias	May occur
6	Reflexes	Hypoactive deep, may be absent
N SPEECH		
		Normal or slow

VII LABORATORY DATA—see 5 VII

VIII ROENTGENOGRAPHIC FINDINGS

A SKULL		
1	Cranial vault	Normal
2	Sella turcica	Normal or enlarged tumor may erode into sphenoid sinus ⁵
3	Mandible	Normal
4	Sinuses	Normal, may have erosion of sphenoid
5	Teeth	Normal
B EPIPHYSEAL STATUS (bone age)		
		Normal unless onset just after puberty then delayed closure
C LONG BONES		
		Normal
D VERTEBRAE		
		Normal
E BONE TEXTURE		
		Normal or osteoporotic
F MISCELLANEOUS		
		May have hypertrophic changes but apparently less often than normal

IX ETIOLOGY

A TUMORS		B MISCELLANEOUS	
1	Craniopharyngioma	1	Pituitary arteries
2	Suprasellar cyst	a	Thrombosis
3	Chromophobe (most common) (see 12)	b	Embolism
4	Acidophilic type in acromegalic patient after	2	Aneurysm of adjacent arteries
a	Intracranial surgery	3	Injury ¹⁷
b	Roentgen therapy	4	Encephalitis
c	Cystic changes	5	Others essentially same as Simmonds disease (see 5 IX)
5	Any growth involving (see Fig 47)	X PATHOLOGY	
a	Pituitary	A GROSS	
b	Hypothalamus	1	Pituitary—as listed under etiology
c	Adjacent areas in brain ¹	2	Thyroid

- 3 Surgical
 - a. Indications
 - (1) Tumor extirpation
 - (2) Biopsy
 - b. Procedure—see 13 VII A

- c. Secondary sex characteristics—not altered
- d. Anemia—the same
 - Tumor may recur in
 - (1) Small percentage
 - (2) Malignant types

VII PROGNOSIS

A INTRASELLAR TUMOR (see 12 IV)

- 1 With roentgen therapy
 - a. Visual field improvement in large percentage
 - b. Headaches partially relieved
 - c. Menstrual periods may return (rarely)
- 2 With extirpation of the tumor
 - a. Intracranial pressure—decreased
 - b. Visual fields—improved

B SUPRASELLAR CYST OR TUMOR

- 1 Relief of headache
- 2 Improvement in visual fields with therapy
- 3 Endocrine status shows little or no improvement

C INACCESSIBLE TUMOR—Poor outcome

VIII CAUSES OF DEATH

A COMPLICATIONS FROM TUMOR

B PNEUMONIA

CHROMOPHOBE ADENOMA

Family history Allergy

Past medical Pneumonia and empyema 2 years ago

Chief complaint Losing weight

History of present illness Patient has had frequent colds since pneumonia. Anemia for 4 years. BP low for years.

Physical examination Age 23 male single. Weight 117 lbs. Height 67 in. BI 98/58. Pallor.

Laboratory data RBC 4,070,000. Hgb 11.7 Gm or 75%. WBC 5056. Differential normal.

Roentgenographic findings Old empyema with thickened pleura.

Treatment Iron.

Progress

YEARS LATER

- 5 Patient was inducted into military service where he developed visual disturbances tingling in his fingers leg cramps and generalized weakness. Skull roentgen film showed an enlarged sella turcica diagnosis pituitary adenoma. Visual fields showed evidence of slight concentric constriction. BMR minus 30 to minus 35%. Roentgen therapy instituted (Testicular biopsy—see below). Testosterone pellets 450 mg inserted. Methyltestosterone 10 mg orally tid for 2 yrs then 1 tablet daily. Also iron and vitamins.

PROTOCOL V FIGS 49-50

- 8 *History* Feels well. Libido improved. Erections each morning and about every 4 to 5 days. Penis seems larger. Shaves every second day. Does not fall asleep any more. More strength. No change in hair.

Physical examination Weight 144 lbs. Height 67¼ in. Pulse 68. BP 110/85. No axillary hair. Scant pubic hair. Beard sparse. Slight prominence of breasts. Penis small. Testes firm. Sella measures 15 x 20 mm or 260 sq mm. No sperm cells in ejaculated specimen.

Laboratory data RBC 4,890,000. Hgb 85%.

GLUCOSE TOLERANCE TEST

Hour	Blood sugar mg %	Serum phosphorus mg %
0	80	3.9
	123	3.3
2	80	3.1
3	81	3.1
4	74	3.3

ADRENAL WATER TEST

Urine volume		
10 00 P.M.—7 30 A.M.		120 cc
8 00 A.M.	Water intake 140 oz	
9 00 A.M.		24 cc
10 00 A.M.		16 cc
11 00 A.M.		24 cc
12 00 NOON		16 cc

- 2 Urinary FSH (male and female) is positive in climacteric
 - 3 Basal metabolism
 - a Normal
 - b Around minus 20 per cent
 - II FUNCTIONAL IMPOTENCE AND FRIGIDITY—All findings as under A
 - C AMENORRHEA—see 61 II
 - D ANOREXIA NERVOSA—see 5 XIV A
 - E SIMMONDS' DISEASE—see 5 XIII
 - F PRIMARY MYXEDEMA—see 25 XIII
 - 1 Skin
 - a Coarse
 - b Dry
 - c Bloated
 - 2 Sex characteristics do not regress
 - 3 Cardiac enlargement
 - 4 Cholesterol (plasma) increased
 - 5 Thyrotropic hormone increased in
 - a Urine
 - b Blood
 - 6 Sella not enlarged unless due to aneurysm of internal carotid
- XV COMPLICATIONS SEQUELAE AND ASSOCIATED DISEASES**
- A CHANGES IN TUMOR
 - 1 Extension
 - a Secondary effects
 - b Intracranial pressure
 - 2 Hemorrhage
 - a Partial blindness
 - b Complete blindness
 - 3 Rupture may improve vision
 - B SEQUELAE
 - 1 Pituitary cachexia and/or hibernation
 - 2 Anemia
 - 3 Loss of sexual function
 - C ASSOCIATED DISEASES
 - 1 Diabetes insipidus
 - 2 Adrenal insufficiency
 - 3 Diabetes mellitus
- XVI TREATMENT**
(see 5 XVI for hormonal therapy)
- A INTRA-SELLAR TUMOR (with no indication of extension) (see II below)
 - 1 Roentgen⁴⁻⁶
 - a Indication—relief of
 - (1) Intracranial pressure
 - (2) Visual defects
 - (3) Hormonal changes
 - b Procedure—see 13 IX A
 - Results (see Fig 49)
 - (1) Favorable changes
 - (a) Visual defects
 - [1] Improved
 - [2] Eliminated
 - (b) Normal catamenia rarely returns
 - (c) Headache relieved
 - (d) General improvement in other symptoms
 - (e) Basal metabolic rate may rise (rare)
 - (f) Sella size may decrease (unusual)
 - (2) Chromophobe tumors are often less radiosensitive than chromophil type several courses at least may be required to produce satisfactory results
 - (3) If no improvement occurs after 3 series, over a period of 5 to 6 months then surgery should be considered
 - 2 Surgical
 - a Indications
 - (1) Intracranial pressure
 - (2) Visual damage which is
 - (a) Severe
 - (b) Progressive (under observation)
 - (3) Neurologic complications—see ventriculography 2 XIII F 6
 - (4) No result from roentgen therapy
 - b Procedure—see 13 VII
 - c Results—see roentgen therapy A 1 c above
 - (1) Tumor may recur
 - (2) Visual damage may become worse
 - (3) Operative fatalities in 5 to 10 per cent
 - B EXTRASELLAR TUMOR (or with intrasellar tumor extension)
 - 1 Ventriculography or encephalography indications—to determine tumor
 - a Size
 - b Location
 - 2 Roentgen
 - a Indication—if tumor is
 - (1) Inaccessible
 - (2) Radiosensitive
 - b Procedure—see 13 IX A

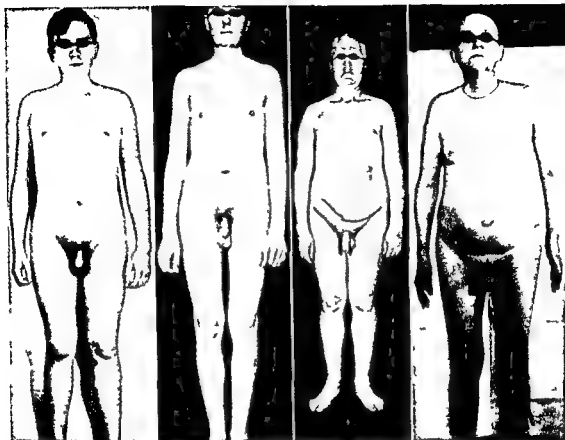


FIG 45 HYPOPITUITARISM DUE TO PITUITARY TUMOR These four cases illustrate the variation in body contours and hair distribution in definite hypopituitarism. Dependence on external characteristics alone is unreliable. All these patients had cranial surgery.

(Extreme left) Panhypopituitarism—chromophobe tumor (verified) *Chief complaints* Headache and failing vision. *Physical examination* Age 20 male hemianopsia no beard body hair present female escutcheon enlarged liver and spleen. *Laboratory data* RBC 4.3 million Hgb 78% plasma cholesterol 191 mg % BMR minus 32%. *Roentgenographic findings* Enlarged sella open radial epiphyses. *Treatment* Cranial surgery.

(Left of center) Panhypopituitarism—mixed tumor (verified) *Chief complaint* Failing vision. *Physical examination* Eyes blind right 50% in left. Skin soft and smooth. Hair silky and fine. Axillary and body hair normal. Female escutcheon. Genitalia slightly below normal. *Laboratory data* RBC 4.0 million Hgb 77% BMR minus 29%. *Treatment* Operation verified mixed type of tumor predominantly eosinophilic in spite of obvious hypopituitarism.

(Right of center) Panhypopituitarism—chromophobe tumor (verified) *Chief complaint* Blurred vision occipital headache fatigue loss of libido. *Physical examination* Age 47 male note body contour female or girdle type of obesity and slight prominence of breasts most likely due to deficient gonadal secretion rather than the direct result of pituitary hypofunction axillary hair present body hair decreased female escutcheon. *Laboratory data* RBC 3.6 million Hgb 84% plasma cholesterol 230 mg % BMR minus 24%. *Treatment* Restoration of vision with roentgen therapy satisfactory sexual function with testosterone pellets.

(Extreme right) Panhypopituitarism—cystic chromophobe tumor. *History of present illness* Baldness present before onset of disorder loss of all other hair mental depression confusion somnolence weakness and anemia for 6 years partial loss of vision for 4 years headache for 1 year. *Physical examination* Age 64 male Eyes right blind left 25% loss of vision. Note fat distribution and prominence of breasts. *Laboratory data* RBC 4.1 million Hgb 83% plasma cholesterol 378 mg % BMR minus 8%. *Treatment* Cranial surgery.

9. Chorionic gonadotropin—2,000 units, 5 times a week, was administered for a period of 3 months. No spermatozoa had been found previously, during or after this treatment. Rather rapid, tender, nodular enlargement of breasts occurred with this medication. Patient gained 3 lbs. Libido was maintained without testosterone.

Comment An example of anemia of obscure origin which eventually was found to be due to hypopituitarism. Patient had loss of libido but did not complain or refer to this, nor did the examining physician inquire about it. The diagnosis was not made until visual disturbance developed. Hyaline change in testes might have been prevented by earlier recognition and treatment. Chorionic gonadotropin maintained sexual function without testosterone did not produce spermatogenesis but caused gynecomastia (see 51 N E 5).

Testicular biopsy

Seminiferous tubules

Number per low power field—70 to 80

Width—one half to one third of normal, distribution uniform

Sertoli cells—present at the narrow lumen

Cells of spermatogenesis—absent or a few spermatogonia (?)

Basement membrane—thin normal. High layer of hyaline mass within the tubules (not around them), between the basement membrane and the Sertoli cells; this layer occupies about half of the tubular space, internal thickening of the basement membrane or intratubular exudate of this membrane and not of the Sertoli cells.

Leydig cells—absent

Interstitial tissue—widened, loose, hyalinized

Blood vessels—normal, congested

Comment Absence of Leydig cells and tubular hypoplasia are typical of hypopituitarism. The hyaline exudate above basement membrane is unusual.

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FIG 4: HYPOPITUITARISM
—GANGLIONEUROMA (verified)

Chief complaints Blurring vision always had oligomenorrhea until onset of amenorrhea and hot flashes 3 years before entry absence of libido recent loss of axillary and pubic hair

Physical examination Age 28 female weight 123 lbs height 59 in bitemporal upper quadrant defects in visual fields fine pale skin infantile cervix

Laboratory data Plasma cholesterol 4 mg %
BMR minus 4%

Roentgenographic finding Sella enlarged

Comment Craniotomy with death from hyperthermia Tumor adhered to optic nerves and third ventricle Hot flashes were experienced with evidence of (neurogenic?) hypopituitarism Patient observed before hormone assays were done

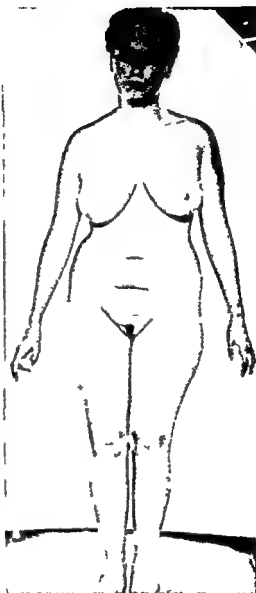




FIG 46 PITUITARY TUMOR EXERTING EFFECT AROUND THE AGE OF 15

History Normal sexual development began between 12 and 13. At 15 voice changed, he began to shave and continued to do so about 3 or 4 times a year. Growth stopped at 18. Libido normal.

Chief complaint Blurred vision in left eye of 6 months duration.

Physical examination Age 21, male, weight 337 lbs, height 76½ in, span 77 in, BP 156/100. Normal body and axillary hair except for female escutcheon, testes and penis but buried in fat.

Laboratory data RBC 4.5 million, Hgb 13.2 Gm.

Röntgenographic findings Skull: no evidence of acromegaly; sella measured 26 x 23 mm with extension into sphenoid sinus. Epiphyses of hands, wrists and iliac crests were closed.

Comment No follow up. Although no further studies could be made, it is obvious from the history that little glandular deficiency was present. Presumably, the tumor did not take place until the age of 15 at least. Family history reveals the background for his size: Father 76 in and large, mother 68 in and stocky. Patient's obesity and over height always has been present. Only evidence of glandular deficiency was the infrequency in shaving. It is not known if a male escutcheon ever had been present. The relationship of his body configuration to the pituitary tumor is difficult to assess.



FIG 49 CHROMOPHOBE TUMOR (See Protocol 4 \ Fig 50) Treatment with roentgen therapy, testosterone and chorionic gonadotropin. The last caused rapid enlargement of breasts. With absence of tubular function gynaecomastia may have resulted by factors postulated in Klinefelter's syndrome.

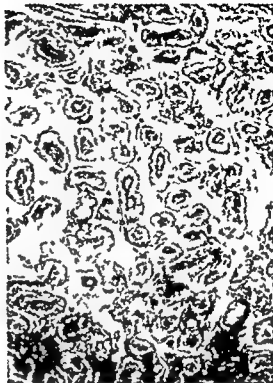


FIG 50 TESTES IN HYPOPITUITARISM (See Protocol 4 \) Note tubular atrophy and absence of Leydig cells (See Fig 49 for details)

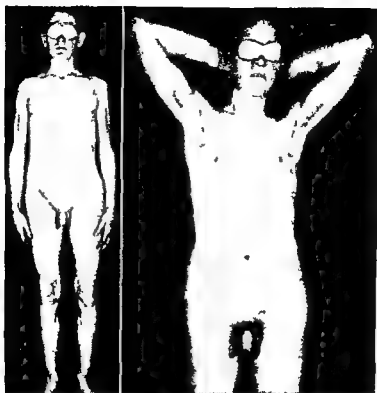


FIG 48 · PANHYPOPITUITARISM — CHROMOPHOBE TUMOR (verified)

(Left) Age 36

Chief complaints Failing vision loss of libido sense of smell and body hair

Findings Bitemporal hemianopsia RBC 4 200 000 Hgb 81%

Plasma cholesterol 326 mg % BMR plus 9%

Operation Restoration of vision rapid recurrence of tumor with failing vision in spite of postoperative radiation successful reoperation with normal vision Persistent hypopituitarism Unable to tolerate 2 gr of thyroid (desiccated USP) daily because of marked weakness

Treatment with testosterone maintained strength 300 mg in pellets lasting from 3 to 4 months 30 mg of methyltestosterone orally and testosterone in glycol alcohol sublingually also effective Hemoglobin unchanged by any form of anti-anemic therapy

(Right) Growth of hair can be seen in left axilla only and greater amounts on the left pubic area from local injection of testosterone in glycol alcohol Seven mg were used daily over a period of 5 months along with 10 mg sublingually for the last 2 months of the same period Excellent response with 15 to 20 mg of Cortisone daily

- D SPINE** Normal or bony structures very evident
- E INTEGUMENT**
- 1 General
 - a Texture Senile changes folds of skin which have been raised remain standing trophic disturbances^{7 11}
 - b Temperature Smooth or senile
Vasomotor disturbances body temperature low—often 95° to 96.8° F (35°C)²⁰
 - c Moisture Absent secretion of sudiferous and sebaceous glands abnormally dry skin occasionally
 - d Eruptions None characteristic
 - e Pigmentation May show light brown or yellow pigment (24%) none of mucous membranes no black freckles
 - f Color Often marked pallor (48%)
 - 2 Hair
 - a Head Normal or prematurely gray may fall out sparse (50%)
 - b Facial Usually scant in males (50%)
 - c Axillary Falls out (80%) if removed may regrow at normal rate
 - d Pubic Falls out (80%)
 - e Body Decreased or absent including lanugo
- F HEAD**
- 1 Shape and size Normal or small features
 - 2 Facial expression Wizenod pathetic or not unusual
 - 3 Eyes
 - a General Normal may appear deep sunken or lifeless
 - b Fundi Normal if tumor present usually optic atrophy²¹
 - c Visual
 - (1) Fields No defects unless due to tumor then usually partial or complete defects bitemporal hemianopsia
 - (2) Acuity Normal or decreased depending on optic findings and progression of severe cachexia
 - 4 Ears and nose Normal
 - 5 Mouth and throat
 - a General Normal may show signs of vitamin B deficiency (smooth beefy tongue cheilosis)
 - b Teeth Carious fall out easily (42%)^{2 22}
 - c Larynx (voice) May be weakened with progression of disease
- G NECK**
- 1 General Thin scrawny chickenlike all underlying structures may be evident
 - 2 Thyroid Small but may be prominent because of tissue wasting
- H CHEST** Thoracic cage is normal or shows all its bony landmarks pleural fluid rarely
- I HEART AND PERIPHERAL VESSELS**
- 1 Heart Size may be smaller than normal (hypoplastic) tones weak distant rarely pericardial effusion²³
 - 2 Rate and rhythm Bradycardia
 - 3 Blood pressure Hypotension usually may have slight increase or normal average 96/62²⁴
 - 4 Peripheral arteries and veins Poor tension
 - 5 Vasomotor Subnormal response to stimulation

SECTION 5

SIMMONDS' DISEASE

SYNONYMS Cachexia hypophyseopriva, Apituitarism, Sheehan's disease

I DEFINITION

A clinical entity characterized by almost total abolition of all the pituitary secretions, which may be rightfully termed apituitarism. The distinction between this disorder and panhypopituitarism is only a matter of degree. The majority of the cases with chromophobe or other tumors do not approach the clinical state described originally by Simmonds.^{50, 51} The greater degree of anorexia and resulting malnutrition may contribute a large part to the clinical findings in Simmonds' disease as compared with other hypopituitary states. Percentages listed below are cited from Escamilla and Lissner (1942).²⁵

II APPEARANCE

Normal early but eventually in some extreme wasting, emaciation, presenescence and retrogression of primary and secondary sex characteristics (see Protocol 5 VI)

III AGE

9 to 69 average 41 years

IV SEX

Females predominate, ratio 7:4

V MENTAL DEVIATIONS

A INTELLIGENCE

Average or subnormal in some cases

B RESPONSIVENESS

Normal or slow, apathic, stuporous

C OTHER ABNORMALITIES

Melancholia, disorientation and often psychosis (over 50%)

VI PHYSICAL STATUS (see Figs 51, 53, 56 and 58)

A NUTRITION

May be exceedingly poor, 'skin and bones', but relatively good in many

1 Weight

Very marked loss or slight amount, average 44 lbs.⁵⁰

2 Fat distribution

Both visceral and subcutaneous fat reduced, often completely gone.¹⁰⁷

B HEIGHT

Normal unless onset before epiphyseal closure, then retarded

C EXTREMITIES

1 Upper

Normal or evidence of extreme cachexia with prominence of all skeletal parts

a Hand

May appear small

b Fingers

Occasionally cyanotic, nails brittle

c Span

Normal

2 Lower

Normal or wasting of muscles and fat with exaggeration of bony skeleton

a Feet

Normal

b Toes

Normal, may show vasomotor and trophic disturbances

C BLOOD CHEMICAL ANALYSES

1 Sugar	Normal, ¹¹¹ but more often decreased, average 66 mg % (Simmonds disease)
2 Nonprotein nitrogen	Normal or slightly decreased
3 Protein	Normal or decreased
4 Uric acid	Normal or decreased ^{10 103}
5 Cholesterol	Normal or decreased, increased occasionally ^{18 1 77 30 3} 23 26 41 73 87 84 94 110 11
6 Sodium	Normal or decreased ^{11 2- 46 88 110 112}
7 Potassium	Variable ^{25 24 84 11}
8 Calcium	Normal ^{14 85}
9 Phosphorus	Normal or decreased ^{10 9 84 94}
10 Phosphatase	Normal or increased ¹⁴
11 Chlorides	Normal, occasionally decreased ^{77 65 56}
12 Iodine	Low organic values ^{84 9 11 113}
13 Creatine	Normal ¹³
14 Creatinine	Normal or increased slightly ¹⁵
15 Carotin	Present ^{1 5}

D FUNCTION TESTS

1 Tolerance (see Chart 17)	
a Glucose	Increased usually (see Table 102 p 1426) ^{11 1 3 77 35-37} 49 50 57 58 61 65-70 79 84 87 88 93 8 94 107 110 117 114
b Glucose insulin	Insulin sensitivity increased ^{1 88}
c Insulin	Normal, delayed or absent rise in blood sugar ^{14 31 5 54} 65 71 84 9 1 12, 112, 113
d Galactose	Normal or high curve ¹⁰⁹
e Iodine	Decreased possibly
2 Adrenal water	Positive usually ^{28 79 80}
3 Salt deprivation	Positive or may be negative ^{77 30 34 63 79 89 93 87 115}
4 Balance	
a Nitrogen	Probably negative but difficult to determine ^{30 110 113}
b Calcium	Probably negative but difficult to determine

E MISCELLANEOUS

1 Basal metabolic rate	Rarely normal usually very low (average minus 35% in Simmonds disease ^{30 117})
2 Circulation time	Normal or increased ^{100 81}
3 Sedimentation rate	Variable ⁴³
4 Specific dynamic action of protein	Normal or decreased (because of lowered BMR) ^{73 77} 31 79 115
5 Gastric analysis	Normal or achylia ^{31 25 6 89 93 11}
6 Electrocardiogram	Normal unless myxedema ⁴³
URINARY HORMONE ASSAYS	
1 FSH	Negative (usually less than 6 mu) ^{1 18 72 23 31 40 41} 45 54 55 68 89 84 107 11 113 rarely may be positive with chromophobe tumor ⁴³
2 LH	No data
3 Estrogens	Decreased or absent ^{18 36 43 46 49 66-68 88}
4 Pregnanediol	Absent ⁴³
5 17 ketosteroids	Absent or very low ^{1 88 27 31 33 33 36 40 45 54 69 68 83 107} 10 106 11
6 11-oxysteroids (glycogenic units)	Very low or absent ^{16, 81 88 107 94}

J BREASTS	
1 Male	Normal
2 Female	Various degrees of atrophy
K ABDOMEN	Ascites may be present ⁷⁴
1 Liver	Not palpable
2 Spleen	Not palpable
3 Hernia	None
4 Tumor	None
L GENITALIA	
1 Male	
■ Penis	Normal or regression in size
b Testes	Variable degrees of atrophy
c Prostate	Atrophic
2 Female	
a External	Atrophic
b Internal	Atrophic
M NEUROMUSCULAR	
1 Muscles	Marked weakness and atonia eventually
2 Gait	Normal or slow and with difficulty, later bedridden
3 Body movements	Normal or labored if extreme cachexia and muscular atonia
4 Tremor	None
5 Paresthesias	Possible
6 Reflexes	Normal or hypoactive
N SPEECH	Normal or slow

VII LABORATORY DATA

A URINE	
1 General	Normal or small amount (unless diabetes insipidus)
2 Special analyses	
a Sugar	None
b Albumin	May be present
c Nitrogen	Normal
d Creatine	Normal or slight decrease
e Creatinine	Normal or slightly increased
f Sodium	Normal
■ Potassium	Normal
h Calcium	Normal
i Phosphorus	Normal
j Iodine	Decreased ⁸⁴
B HEMATOLOGY	
1 Red blood cells	Normal or decreased in prepubertal hypopituitarism usually decreased 3 to 4 million in adults (see Protocol 5 V) ⁸⁵
2 Hemoglobin	Normal or decreased in prepubertal cases. Simmonds' disease in adults average 65 per cent chromophobic tumor average 85 per cent (see 13 III B) ⁸⁵
3 White blood cells	Normal or decreased ^{75 87 89 9}
4 Differential	Monocytes or microcytes; eosinophils increased (average 6.3% in Simmonds' disease) relative lymphocytosis and neutropenia ^{3 7 8 87 89}
5 Color index	Normal or decreased ⁸⁹

X PATHOLOGY²⁵

A GROSS

1 Pituitary

- a Normal gland occasionally, but always associated with definite pathology at

- (1) Tuber cinereum
- (2) Hypothalamus

- b Necrosis (Sheehan's disease) frequently develops after postpartum following^{10 1 9 71 87 94}

- (1) Ischemia
- (2) Embolic infarction

- c Atrophy

- d Cyst of Rathke's pouch or cranio-pharyngioma

- e Hemorrhage

- f Thrombosis

- g Aneurysm

- h Neoplasms

- (1) Primary
 - (a) Pituitary (unusual)
 - (b) Extrasellar
 - [1] Infundibular
 - [2] Glioma
 - [3] Endothelioma
- (2) Secondary (metastatic)

- i Sclerosis

- j Fibrosis

- k Abscess

- l Inflammations

- m Adenomas

- (1) Chromophobic
- (2) Basophilic

- n Tuberculosis (rare)

- o Syphilis (uncommon)

- 2 Other organs—generally show signs of atrophy and/or fibrosis (splanchno-mia)

B MICROSCOPIC

- 1 Pituitary—see 2 IX B

- a Findings depend on gross pathology

- b If any pituitary cells remain they are⁸⁷

- (1) Mostly chromophobes
- (2) Few chromophils

- 2 Bone marrow¹⁰³

- a Inactive

- b Eosinopenia

XI PATHOLOGIC PHYSIOLOGY

A GROWTH HORMONE

- 1 It is unknown if this hormone is elaborated in a normal person after longitudinal development ceases
- 2 If this is true a deficiency or absence of growth hormone must play a role in the hypopituitary state causing some anabolic failure

B GONADOTROPIC HORMONES

- 1 Degree of decreased function is variable
- 2 Usually first hormonal deficiency to be manifested clinically

C THYROTROPIN

- 1 Secretion reduced
- 2 Pituitary myxedema is rare

D ADRENOCORTICOTROPIC HORMONE

- 1 Secretion is decreased generally
- 2 Severe crises of Addison's disease are rare possibly due to a higher functional level in the latter of the⁴³
 - a Pituitary
 - b Thyroid
- 3 Axillary, pubic or facial hair may persist with an absent or ineffectual gonadotropin secretion (even with a pituitary tumor) due to some adrenal secretion
- 4 Adrenal water test may still be positive

E PREDOMINANT HORMONAL DEFICIENCIES

- 1 Selective deficiency of one pituitary hormone is exemplified by FSH negative eunuchoidism
- 2 Predominant deficiency of one or more hormones in panhypopituitarism seems likely (see 6 7)

F MISCELLANEOUS

- 1 Cachexia due to marked or complete deficiency of pituitary hormones is a complex problem in this disease
- 2 Anorexia undoubtedly contributes to final state through inadequate (see 103 XIV)
 - a Nutrition
 - b Vitamins
 - c Amino acids
 - d Enzymes
- 3 Carbohydrate metabolism (see 103 I J 1)
 - a Tolerance greatly increased
 - b Liver glycogen deposition enhanced

7 Aschheim Zondek	Negative
8 TSH	Decreased or absent ^{10 40 41 III 112}
9 Corticotropins	Absent ⁴⁰
G BIOPSY	
1 Endometrial	Hypoplasia or atrophy
2 Testicular ⁴²	
a Tubules	Hypoplastic or atrophic
b Leydig cells	Absent
c Spermatogenesis	Arrested
H VAGINAL SMEAR	Atrophic, variable amounts of glycogen ⁴³
I SEMEN ANALYSIS	Aspermia

VIII ROENTGENOGRAPHIC FINDINGS

A SKULL	
1 Cranial vault	Normal
2 Sella turcica	Normal enlarged or unusually small (occasionally intrasellar or suprasellar calcareous deposits destruction possible) ^{29 33 101}
3 Mandible	Normal ^{40 9 116}
4 Sinuses	Normal, underdeveloped in prepuberal cases
5 Teeth	Carious in some cases, normal dental age in prepuberal hypopituitarism ⁴³
B EPIPHYSEAL STATUS (bone age)	Normal, retarded if onset before adolescence (see Fig. 57) ^{4 43}
C LONG BONES	Normal
D VERTEBRAE	Normal, decalcification reported ⁴¹
E BONE TEXTURE	Normal
F MISCELLANEOUS	None

IX ETIOLOGY⁷⁵

A FOLLOWING PREGNANCY (see Figs 53 and 58)	
1 Puerperal sepsis	9 Dysentery
2 Prolonged and difficult labor with or without severe hemorrhage (see Protocol 5 VII to V)	10 Encephalitis
3 Repeated conceptions	11 Catarrhal jaundice
4 Toxemia	12 Tuberculosis ⁷³
	13 Syphilis
B INFECTIOUS PROCESSES (not associated with pregnancy)	
1 Meningitis	C MISCELLANEOUS
2 Pulmonary infection	1 Postoperative hypophysectomy
3 Tularemia	2 Aneurysm of adjacent arteries ⁴³
4 Malaria	3 Skull fracture with
5 Influenza	a Hemorrhage at midbrain
6 Osteomyelitis	b Posttraumatic arteriovenous aneurysm ⁷⁶
7 Diphtheria	4 Tumors
8 Rheumatic fever	a Primary
	(1) Intrasellar
	(2) Extrasellar
	b Secondary metastatic
	5 Old age ⁷⁷
	6 Intensive pituitary radiation (rare)
	7 Idiopathic (see Fig 56)

- d Weight
 - (1) Changes are not diagnostic
 - (2) Patient may secretly discard feedings
 - e Skin shows less change may be
 - (1) Rough
 - (2) Scaly
 - f Pallor—usually absent
 - g Temperature may be subnormal (15%)
 - h Hair—less frequently affected (15%) at
 - (1) Pubis
 - (2) Axillae
 - i Teeth do not
 - (1) Decay
 - (2) Fall out
 - j Breasts—atrophy proportionately
 - k Eosinophilia—absent
 - l Chlorides (serum)—decreased¹⁰⁰
 - m Water test
 - (1) Normal (mild cases)
 - (2) Positive (severe cases as in Simmonds disease)
 - n Response to ACTH test
 - o Lower values than Simmonds disease for
 - (1) 17 ketosteroids
 - (2) Cortin (glycogenic units)
 - p Sella never is
 - (1) Deformed
 - (2) Calcified
 - q Average duration 2 ½ years
 - r Response to adequate nutrition
 - (1) Final diagnostic sign in many
 - (2) Patient may require
 - (a) Tube feedings
 - (b) Intravenous fluids
 - (c) Vitamin supplements
 - s Simultaneous hormone therapy as used in Simmonds disease
 - (1) Recovery may be hastened
 - (2) Unnecessary to continue with this if sufficient caloric intake can be maintained
 - t Comment
 - (1) Anorexia nervosa may be indistinguishable from Simmonds disease (see Protocol 5 VIII)
 - (2) If recovery is obtained by any means and maintained subse-
quently on adequate nutrition only a diagnosis of anorexia nervosa is then justified
- II PRIMARY MYXEDEMA (see 25 VIII)
 - 1 Weight loss is not common
 - 2 Hair
 - a Very fine
 - b Scant
 - 3 Face
 - a Bloated
 - b Puffy
 - 4 Edema nonpitting
 - 5 Heart size may be increased
 - 6 Secondary sex characteristics usually not affected
 - 7 Genital organs show no atrophy
 - 8 Cholesterol (plasma)—high
 - 9 Water test—normal, occasional exception⁴³
 - 10 Electrocardiogram—abnormal
 - C ADDISON'S DISEASE
 - 1 History of
 - a Tuberculosis in many patients
 - b Remissions
 - (1) Vomiting
 - (2) Diarrhea
 - c Acute crises
 - 2 Catamenia is present in majority
 - 3 Presenescence is not found
 - 4 Black freckles
 - 5 Pigmentation of
 - a Mucous membranes
 - b Exposed areas
 - c Parts subject to friction
 - 6 Hair is less affected
 - a Beard
 - b Axillary (infrequently lost)
 - c Pubic (rarely falls out)
 - d Body
 - 7 Lymph glands are palpable
 - 8 Hematocrit—increased
 - 9 Water test—positive
 - 10 No response to ACTH test
 - 11 Basal metabolic rate
 - a Normal
 - b Decreased slightly
 - 12 Urinary FSH—increased if after meno-
pause
 - 13 17 ketosteroids
 - a Variable
 - b Subnormal usually
 - 14 Sella—normal
 - 15 Adrenals may be calcified
 - D TUBERCULOSIS
 - 1 Lesion may be located
 - 2 Febrile course
 - 3 Aging not evident

- c Insulin secretion is apparently unchanged

G REGENERATION OF PITUITARY TISSUE

- 1 Postpartum necrosis of pituitary may be followed by regeneration of tissue, especially if subject becomes pregnant (unlikely)■
- 2 This does not occur with other pathologic changes

XII SYMPTOMATOLOGY

A COMMENT

- 1 If tumor and/or intracranial pressure—see 13 VI
- 2 Many of the following symptoms do not occur initially, but may develop gradually with progression of the disorder

B NEUROMUSCULAR

- 1 Wasting, marked
- 2 Cachexia
- 3 Fatigue, excessive
- 4 Weakness
- 5 Prostration
- 6 Muscular
 - a Atonia
 - b Atrophy
- 7 Headache
- 8 Vertigo
- 9 Fainting
- 10 Cold sensitivity
- 11 Dull
- 12 Drowsiness
- 13 Confusion
- 14 Disorientation
- 15 Depression
- 16 Irritability
- 17 Coma (hypoglycemia 5%)

C GASTRO INTESTINAL

- 1 Anorexia, marked
- 2 Dyspepsia
- 3 Constipation
- 4 Diarrhea
- 5 Abdominal pain
- 6 Vomiting
- 7 Weight loss (not diagnostic)

D GENITO URINARY

- 1 Amenorrhea
- 2 Loss of libido
- 3 Impotence
- 4 Genital atrophy
- 5 Sterility
- 6 Polyuria
- 7 Oliguria

XIII DIAGNOSIS

- A COMMENT—The early diagnosis may be difficult but is to be entertained if a majority of the following are found

B SYMPTOMATOLOGY

- 1 History of severe past illness, especially postpartum hemorrhage (see 5 IX A)■
- 2 Amenorrhea
- 3 Sexual function lost
- 4 Cachexia, varying degree

C SIGNS

- 1 Hypotension
- 2 Skin is smooth
- 3 Pallor
- 4 Sexual hair is shed

D LABORATORY DATA

- 1 Blood count
 - a Anemia
 - b Relative lymphocytosis
 - c Eosinophilia
- 2 Glucose tolerance—increased
- 3 Insulin sensitivity—increased
- 4 Water test—positive
- 5 ACTH test—variable
- 6 Basal metabolic rate—low
- 7 17 Ketosteroids
 - a Low
 - b Absent

XIV DIFFERENTIAL DIAGNOSIS

A ANOREXIA NERVOSA (see Fig 55)¹⁰

- 1 The eventful extreme undernutrition in many cases leads to a physiologic failure of the anterior pituitary, which is often indistinguishable from "organic" hypopituitarism
 - 2 The following data may be helpful in solving the problem
 - a Type of individual
 - (1) Young (average age 21)
 - (2) Single
 - (3) Females predominate (ratio 9:1)
 - b History of
 - (1) Mental shock
 - (2) Psychosis
 - (3) Inferiority complex
 - (4) Postpartum hemorrhage may not be obtained
 - (5) Asthenia which is not as severe
- Precocious senescence is less evident (5%)

- b Comment
 - (1) Theoretically might be helpful because of anabolic effects
 - (2) Pure growth hormone is not available commercially
- 2 Testosterone⁹ 1 25 46 54 110 113
 - a Indications
 - (1) Advisable in most cases with initial treatment
 - (2) Promotion of anabolic effects (males and females)
 - (3) Weight gain
 - (4) Improvement of strength
 - (5) Protection against thyroid crisis from administration of desiccated thyroid
 - (6) Primary or secondary sex characters may progress
 - (7) Spermatogenesis may occur¹⁵ 3
 - b Dosage
 - (1) Oral or sublingual—methyltestosterone 15 to 30 mg daily
 - (2) Intramuscular—testosterone propionate, 50 to 150 mg weekly
 - (3) Pellets—testosterone, 150 to 300 mg every 2 to 4 months
 - c Results
 - (1) General improvement in
 - (a) Strength
 - (b) Energy
 - (2) Partial regrowth of hair (in order of appearance)
 - (a) Beard
 - (b) Axillary
 - (c) Pubic
 - (d) Body
- 3 Desoxycorticosterone acetate (DOCA) (synthetic)² 41 51 113 115
 - a Indications
 - (1) Hypotension
 - (2) Asthenia
 - (3) To improve metabolism of
 - (a) Salt
 - (b) Chloride
 - (c) Carbohydrate (possibly)
 - b Dosage—pellets 150 mg until absorbed may last for 6 to 15 months
 - c Results
 - (1) Generally better
 - (2) Weight gain
 - (3) Blood pressure increases
 - d Treatment of overdosage (see 40 XVI D)
 - (1) Remove pellets if necessary
 - (2) Ammonium chloride (enteric coated)—oral 60 to 90 gr daily
 - (3) Potassium citrate (20% solution)—oral, 4 to 8 cc in fruit juice daily
- 4 Thyroid (desiccated, U S P)¹³ 15 3 11
 - a Indication—advisable only after a month or so of treatment with
 - (1) Desoxycorticosterone
 - (2) Testosterone
 - b Dosage—oral 1 to 2 gr daily
 - c Results
 - (1) Most effective with evidence of pituitary myxedema
 - (2) Some patients may not tolerate drug
- 5 Cortisone
 - a Indications
 - (1) Supplement to above program
 - (2) As sole therapy
 - b Dosage oral—10 to 25 mg /24 hrs
 - c Results
 - (1) As for ACTH (see below)
 - (2) Cessation of therapy not followed by sudden relapse
- 6 Adrenocorticotrophic hormone¹¹ 41 104
 - a Indication—trial worth while because of possible stimulation of natural adrenocortical factors
 - b Dosage—parenteral (see 106 III E 7)
 - (1) Initial—40 mg daily increase to effective dosage
 - (2) Maintenance—by trial and error
 - (3) Testosterone should be administered simultaneously
 - c Results
 - (1) Well being returns
 - (2) Mental improvement
 - (3) Appetite stimulated
 - (4) Weight increased
 - (5) Breasts develop (female)
- 7 Gonadotropins
 - a Indications
 - (1) Rarely if ever necessary
 - (2) Preferably used after
 - (a) Testosterone
 - (b) Desoxycorticosterone
 - b Dosage—parenteral
 - (1) Chorionic gonadotropin—500 to 1 000 ru daily¹⁵ 31 60 67 116

- 4 Advanced stages diagnosis obvious
 - 5 *Tubercle bacillus* often isolated
 - 6 Negative results for adrenal insufficiency, except possibly the water test
 - 7 17 ketosteroids—more normal
- E MALIGNANCIES**
- 1 Lesion often discovered
 - 2 Presenescence absent
 - 3 Obvious in advanced stages
 - 4 17 ketosteroids—normal
- F HYPERTHYROIDISM (see 26 VIII)**
- 1 Skin
 - a Moist
 - b Warm
 - 2 Sexual hair—normal
 - 3 Thyroid gland—enlarged
 - 4 Blood pressure—normal for age
 - 5 Pulse pressure—wide
 - 6 Sexual organs—normal
 - 7 Tremor—present
 - 8 Cholesterol (plasma)—low
 - 9 Iodine (blood)—increased
 - 10 Basal metabolic rate—elevated
 - 11 Hyperthyroidism and Addison's disease may coexist
- G ANEMIAS**
- 1 Skin texture—normal usually
 - 2 Hair growth—not affected
 - 3 Sexual organs—normal
 - 4 Basal metabolic rate—normal in most cases
 - 5 Sprue
 - a Liver and/or spleen may be palpable
 - b Macrocytic anemia
 - Stools
 - (1) Fatty
 - (2) Loose
 - d Calcium (serum)—may be low
 - e Water test—positive
 - 6 Pernicious anemia (rarely associated disease)⁴⁹
 - a Spleen and/or liver may be palpable⁵⁰
 - b Macrocytic anemia
 - c Posterior lateral column degeneration possible
 - d Urobilinogen excretion—increased
 - e Response to liver injections
- H OTHER DISEASES**
- 1 Pellagra
 - a Hair—normal
 - b Dermatitis—common at exposed surfaces
 - c Sexual organs—normal
 - d Basal metabolic rate—normal
 - Response to therapy
 - 2 Pituitary myxedema (see 6)
 - a Cholesterol (plasma)—high
 - b Electrocardiogram may be
 - (1) Normal
 - (2) Abnormal
 - 3 Chronic ulcerative colitis or ileitis
 - a Diarrhea
 - b Lesion can be localized
 - Fever
 - d Fingers clubbed
 - Secondary effects of pituitary dysfunction may be present
 - f Sedimentation rate—increased
 - g Water test—positive as in Simmonds disease
- XV COMPLICATIONS SEQUELAE AND ASSOCIATED DISEASES**
- A INTERCURRENT INFECTIONS**
- B HYPOGLYCEMIC ATTACKS^{25, 11}**
- C DIABETES INSIPIDUS⁵¹**
- D ADRENOCORTICAL CRISES**—May occur depending on degree of secondary adrenocortical atrophy
- E DIABETES MELLITUS (rare)^{7, 29}**
- F PERNICIOUS ANEMIA (infrequent)³⁰**
- G ARTHRITIS hypertrophic or rheumatoid (see Fig 54)**
- XVI TREATMENT**
- A OBJECTIVES**
- 1 Substitution for the various glandular deficiencies to
 - Improve patient's strength
 - b Prevent hypoglycemic reactions
 - c Restore sexual function (of secondary importance)
 - 2 If pituitary tumor is present (and following the above program)
 - a Roentgen therapy to decrease its size (see 13 IX)
 - b Surgical removal if indicated (see 13 VII)
- B GENERAL MANAGEMENT**
- 1 Growth hormone
 - a Dosage—intramuscular, 10 ru (1 cc) or more daily

(2) Tumor is not

- (a) Ingressing
- (b) Inaccessible

b Successful maintenance in moderately deficient cases

c Correction of the following in various degrees

- (1) Anemia
- (2) Fatigability
- (3) Metabolic rate

3 Comment

- a Therapy with testosterone desoxy corticosterone and desiccated thyroid is now relatively inexpensive
- b After treatment over a period of a year or so some cases may get along on surprisingly little therapy.¹¹

XVII PROGNOSIS

A FACTORS

1 Etiology

2 Response to therapy

B OUTLOOK

- 1 In past—poor
- 2 Present age—favorable

C TYPE OF CASE

- 1 Acute—death within a few months unless adequate therapy
- 2 Chronic^{10 86 11 100}
 - a Incidence—more common
 - b Range—11 to 44 years (untreated)
- 3 Sheehan's disease⁶⁴
 - a Spontaneous recovery reported
 - b Subsequent pregnancy (if possible) believed by Sheehan to stimulate regeneration of pituitary

XVIII CAUSES OF DEATH

A TUBERCULOSIS

B COMA (adrenal hypoglycemia)

C BRONCHOPNEUMONIA (terminal)

SIMMONDS DISEASE
ASSOCIATED WITH PITUITARY TUMOR

Family history Tuberculosis cardiovascular disease

Past medical Normal until 30 years old

Chief complaint Tires very easily

History of present illness Amenorrhea fatigability and weakness for 18 years Fifteen years ago diagnosis of pernicious anemia Liver and iron given the latter for 10 years without benefit External strabismus developed 14 years ago Anorexia Hair has become dry and falls out Voice has changed Cold sensitivity for 5 years Mental sluggishness Thyroid 1 gr every other day About a year preceding admission pains and numbness occurred in her feet and legs She was unable to walk for 4 days

Physical examination Age 48 female single Weight 102 lbs Height 52½ in Pulse 96 BP 132/82 Skin pale yellowish tinge dry coarse Hair not remarkable Eyes puffy left external strabismus Normal visual acuity and fields Husky voice Cold hands and feet Slow movements Hypoactive reflexes

Laboratory data Urine albumin 1 plus RBC 4 280 000 Hgb 11.8 Gm (84%) WBC 8 700 Differential polymorphonuclears 76% lymphocytes 17% monocytes 6% eosinophils 1% Blood sugar 80 mg %

NPV 28 mg % Plasma cholesterol 191 mg % Serum phosphorus 3.8 mg % Water test positive Sedimentation rate 50 mm /hr EKG left axis deviation 17 keto steroids 1.0 mg /24 hrs (500 cc)

Röntgenographic findings Skull—lateral area of sella turcica measures 344 sq mm on left and 228 sq mm on right thinning of dorsum sellae and depression of floor into sphenoid sinuses anterior clinoids are intact but right anterior clinoid appears elevated Chest—some fibrosis and thickened pleura in both apical regions lungs and heart normal

Treatment Desoxycorticosterone (DOCA) 1 pellet (75 mg) Testosterone 2 pellets (75 mg each) Thyroid (desiccated USP) ¼ gr daily then increased to ½ gr daily for 2 weeks 1 gr daily next 2 weeks Frequent meals of low carbohydrate and high protein Salt liberally

Progress notes Improved a great deal in 3 months Weight 108 lbs Pulse 80 BP 130/80 Thyroid 1 gr daily Desoxycorticosterone and testosterone pellets still present

Comment Hypopituitarism due to pituitary tumor which because of the weight loss and marked asthenia may be diagnosed Sim

- (2) Anterior lobe gonadotropins—
100 to 300 r u daily^{1 4 5 8 17}
18 30 31 39 42 ■ 61 66-68 77 78
90 116 117
- c Results^{6 17 23 ■ 7 78 79 81 116}
- (1) Most effective when combined (chorionic and anterior lobe gonadotropins⁴³)
 - (2) Value questionable in females
 - (3) Stimulation of testes to testosterone production is possible (see Protocol 5 I \)
- 8 Estrogens⁹³
- a Indications—amenorrhea
 - b Dosage
 - (1) Oral
 - (a) Stilbestrol—0.5 to 1.5 mg daily
 - (b) Estrone sulfate—0.3 to 1.2 mg daily
 - (c) Other preparations in comparable dosage
 - (2) Parenteral—estradiol benzoate 10,000 to 50,000 I U weekly
 - c Results
 - (1) Questionable value
 - (2) Production of periodic menstrual bleeding possible (see 61 II E 4 for use of progesterone)
- 9 Adrenalin
- a Indications
 - (1) Hypoglycemic shock
 - (2) Adjunct to other therapy in acute crisis
 - (3) Rarely necessary
 - b Dosage—subcutaneous 0.5 to 1 cc as indicated
 - c Result—helpful in some
- 10 Protein hydrolysate or amino acids
- a Indications
 - (1) Protein intake decreased
 - (2) Severe cachexia
 - b Dosage—up to equivalent of 70 Gm of protein daily
 - Results
 - (1) Utilization may be inadequate but more likely than from ingested proteins
 - (2) Other therapy may enhance their effects
- 11 Glucose
- a Indications
 - (1) Acute crisis
 - (2) Hypoglycemic shock
 - b Dosage—intravenous, 5 to 10 per cent solution in saline
 - Results—may be very beneficial
 - d Caution—severe hypoglycemia may follow
- 12 Salt
- a Indications
 - (1) As an adjunct to desoxycorticosterone (DOCA), but rarely necessary
 - (2) Intravenously in acute crisis but not often required
 - b Dosage
 - (1) Oral—3 to 6 Gm daily
 - (2) Intravenous—2,000 cc physiologic saline with 5 per cent glucose
 - c Results
 - (1) Doubtful
 - (2) Possible edema from overdosage
- 13 Diet
- a Hypoglycemic shock may be prevented by
 - (1) High protein intake
 - (2) Decreased carbohydrates
 - b Feedings—frequent
 - c Vitamin content—high
 - d Caloric intake—3,200
 - Potassium foods—theoretically low
- C SUMMARY
- 1 General therapy
 - a Hypoglycemic shock
 - (1) Adrenalin
 - (2) Glucose in saline (intravenous)
 - b Acute adrenal insufficiency
 - (1) Adrenocortical hormone
 - (2) Cortisone
 - (3) Desoxycorticosterone acetate (DOCA)
 - (4) Glucose in saline (intravenous)
 - c Chronic cachexia
 - (1) Testosterone
 - (2) Desoxycorticosterone acetate (DOCA)
 - (3) Thyroid
 - (4) Cortisone
 - (5) Adrenocorticotropin
 - (6) Adequate salt intake
 - (7) Other therapy
 - 2 Results from hormonal therapy
 - General improvement when
 - (1) Infection (severe) does not complicate problem

Röntgenographic findings: Skull normal
Lungs clear
Progress: With psychiatric treatment and adequate diet, patient gained 25 lbs in 6 months. Menses returned. Mental problems resolved. Enjoyed good health.
Comment: Amenorrhea, weight loss and low

17 ketosteroids suggest possibility of hypopituitarism; however there was no loss of sexual hair, the adrenal water test was normal and with an adequate diet normal health was restored. Some deficiency of pituitary function may have existed as result of starvation.

SIMMONDS' DISEASE²⁹

Family history: Brother 72 in, father 69 in, all his sisters are tall (one is 63 in.)

Past medical: Asthma

Chief complaint: Gland trouble

History of present illness: Normal growth and development up to 16 or 17 years of age, none since. Sluggish and tires easily. No beard. Skin dry. Voice remained puerile. Semisoft erections. Partial loss of libido. Testosterone injections 1 year before admission. 50 mg a week for 3 months. Sexual hair appeared for first time, and penis became larger. Sexual desires increased, some success at intercourse.

Physical examination: Age 43, male, married (at age 35). Weight 143 lbs. Height 60½ in. Span 67 in. Pulse 56. BP 120/80. Well developed and nourished, very youthful as in early twenties. Voice puerile. Skin smooth, fine, dry. Scalp hair fine and thin. Beard absent. Fine fuzz on chest. Scant axillary and pubic hair. Testes and penis adolescent size. Prostate very small.

Laboratory data: Urine normal. RBC 4,150,000. Hgb 12.4 Gm. WBC 4,100. Differential polymorphonuclears 47.5%, lymphocytes 40%, monocytes 6%, eosinophils 7.5%. Plasma cholesterol 264 mg % BMR minus 23%. Urinary hormones: FSH negative (unconcentrated) and 17 ketosteroids 3.6 mg/24 hrs. No sperm seen in ejaculate.

Röntgenographic findings: Bone age 16 years. Degenerative arthritis of cervical spine. Normal sella, area 67 sq mm.

MONTHS

Up to Chorionic gonadotropin (self administered)—1,000 units 5 days a week for 34 months with an occasional lapse of several weeks. Methyltestosterone—10 to 20 mg daily for 34 months discontinued at times to test effectiveness of chorionic gonadotropin. Desiccated thyroid—½ gr during last 24 months.

PROTOCOL IX Figs 56-57

of above period. 17 ketosteroids at 28 months—3.2 mg/24 hrs. at 31 months—4.0 mg/24 hrs. Urinary FSH at 28 months positive (on APL). Increase of all sexual hair. Penile erections and libido. More endurance. No sperm in semen specimen at 30th and 34th months.

34 to Methyltestosterone, 10 mg daily.
39 Height 60½ in. Shaves every other day. Testes larger. Wife became pregnant. Adrenal water test positive. Urinary FSH negative. 17 ketosteroids at 37th month 3.6 mg/24 hrs. Total sperm count 50,000,000, lively and appeared fairly normal. Radial epiphyses closed.

44 Total sperm count 90,000,000. 90% motile, 30% normal morphology, 50% minor defects, remainder markedly abnormal. Testosterone pellets 150 mg. No thyroid given.

47 Semen specimen 850,000 sperm/cc. 10% motile, large round heads in 90%. Wife had a normal boy. Patient still takes methyltestosterone 10 mg daily and desiccated thyroid ½ gr daily.

65 On 15 mg methyltestosterone daily, total sperm count was 112 million. Majority of nonmotile forms were abnormal including wry necks, double collars, pinheads, large and small round heads. 25% motile (condom specimen). No desiccated thyroid for 5 weeks. Plasma cholesterol 316 mg % BMR minus 20%. Total eosinophil count 343/cu mm. Excellent health.

Comment: This case illustrates midpuberal hypopituitarism in a 43-year-old man beginning about 15 to 16 years of age. Therapy with chorionic gonadotropin, methyl

monds' disease This case also illustrates one of the causes of obscure and resistant anemia for which the patient had 15 years of treatment Although the sella was enlarged, no visual field defects were noted External strabismus undoubtedly due to

pressure on the sixth nerve Response to hormonal therapy was excellent Patient's improvement maintained during the following 2 years Roentgen therapy and possibly surgery at later date were advised No follow up

SHEEHAN'S DISEASE

Family history Irrelevant

Past medical Negative

Chief complaint Mental depression

History of present illness At age of 31, after her youngest child was born, patient had a severe postpartum hemorrhage with shock and unconsciousness Since that time she became progressively weak and tired, her menstrual periods never returned, and all body and sexual hair disappeared Treated for anemia Given thyroid periodically Hips became stiff and her gait was awkward No hot flashes

Physical examination Age 67, female married Weight 84 lbs Height 54 in Pulse 96 BP 115/70 Marked pallor Skin dry and cold Motions and speech slow Practically no abduction of hips and only 5° to 10° adduction

Laboratory data RBC 4 340 000 Hgb 12.4 Gm WBC 8 000 Fasting blood sugar 98 mg % Plasma cholesterol 281 mg % Adrenal water test positive Sedimentation rate 54 mm/hr BMR minus 25% EKG showed inverted T T₃ 17 ketosteroids 4.5 mg/24 hrs

Röntgenographic findings Skull—calcification in right frontal region above anterior

PROTOCOL VII Figs 52-54

clinoid process Sella—normal in size Pelvis—advanced degenerative arthritis of hip joints and lower spine Ischial bursitis

Treatment and progress Three pellets (225 mg) of testosterone propionate and 1 pellet (75 mg) of desovycorticosterone (DOCA) implanted

MONTHS

1 Thyroid (desiccated, USP) 1 gr orally daily

9 Weight 90 lbs BP went to 160/90 Regrowth of pubic hair and increase in body hair Patient comparatively well

11 Patient began to lose weight down to 83 lbs Anorexia and weakness BP 110/80 Total eosinophil count 380/cu mm 150 mg each of testosterone and desovycorticosterone pellets implanted Improvement in 10 days

Comment A case of Sheehan's or Simmonds disease with disability for 36 years, successfully treated with testosterone desovycorticosterone and thyroid It is of special interest to note the development of hyper trophic arthritis in panhypopituitarism Cortisone 125 mg/24 hrs, has since been additionally helpful in this case

ANOREXIA NERVOSA

Family history Negative

Past medical Negative

Chief complaint Loss of weight and energy

History of present illness Many emotional conflicts Believed that hips and feet were enlarging and that weight reduction was imperative Usual weight 130 lbs Reduced food intake, forced herself to vomit used cathartics and punctured nasal septum believing these would hasten weight loss Periods scanty, then amenorrhea past 2 months Patient wished to gain weight without hips enlarging (conflict)

PROTOCOL VIII FIG 55

Physical examination Age 19, female single Weight 69 lbs Height 61 in Pulse 44 BP 70 systolic indefinite diastolic Temperature 96° Looked older than her age Gaunt expression Skin dry coarse cold Axillary and pubic hair present No pigmentation present

Laboratory data Urine negative RBC 3 600 000 Hgb 84% WBC 6 350 Adrenal water test negative Sedimentation rate 2 mm/hr Urinary hormones FSH negative (unconcentrated) pregnandiol negative 17 ketosteroids 4.6 mg/24 hrs

- bestrol No change in blood counts or treatment
- 52 Bad head cold and influenza House More pubic hair and lanugo over entire body Intense dislike for meat and eggs Weight 118 lbs Thyroid pills stopped Pulse 62 BP 100/90 lying down, could not be recorded while standing Temperature 97° No change in blood counts Serum phosphorus 2.8 mg % Plasma cholesterol 269 mg % Testosterone, 2 pellets (75 mg each) Desoxycorticosterone 2 pellets (75 mg each) To take daily thyroid 2 gr feosol 15 gr stilbestrol, 0.5 mg orally benzedrine 5 mg essessamide 6 teaspoonfuls
- 64 Much stronger No catamenia or libido Stilbestrol stopped Pubic hair increased and new axillary hair appeared Not sleepy Weight 118 lbs Pulse 64 After resting BP 140/150/100 Temp

perature 97.6° RBC 4 000 000 Hgb 11.2 Gm Eosinophils 4.5% Plasma cholesterol 123 mg % Testosterone, 2 pellets (75 mg each) Desoxycorticosterone, 1 pellet (75 mg) All other medication discontinued

76 Color better More pubic hair Gained to 130 lbs Fingers became swollen after omitting thyroid Present weight 123 lbs BP 130/100 Hgb 11.2 Gm (80%) Plasma cholesterol 121 mg % Thyroid 1 gr daily

Comment Classical symptoms and physical signs of Simmonds disease following post partum necrosis of anterior pituitary carcinoma of stomach She had amenorrhea loss of pubic, axillary and body hair, anorexia weight loss weakness hypoglycemic coma, anemia and a low BMR without myxedema Response to treatment very satisfactory Cortisone 15 mg daily has greatly helped this patient

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testosterone and desiccated thyroid produced return of normal libido potentia and spermatogenesis Successful impregnation of wife and delivery of a normal baby Adrenal water test positive, yet general

strength and endurance excellent 17 ketosteroids always low Chorionic gonadotropin did not increase the 17 ketosteroid output in spite of its apparent effect on hair growth and erections

SHEEHAN'S DISEASE

Protocol X Fir 58

Family history Cardiovascular disease and stomach ulcers

Past medical Essentially negative Married 8 years One child 7 years old second 4 years old third pregnancy a miscarriage

Chief complaint Asthenia and anorexia for 6 months

History of present illness Patient became pregnant 9 months before admission and had a threatened abortion in the third month After a hard labor she had a still birth and a severe postpartum hemorrhage requiring ten transfusions Vomited constantly Her skin peeled Since that time marked fatigue dyspnea on exertion low back pain, falling hair difficulty in swallowing, anorexia and weight loss of 17 lbs Bleeding piles occasionally Amenorrhea for 8 months

Physical examination Age 32 years, female married Weight 118 lbs BP 116/80 Pulse 80 Well developed and nourished Appeared prematurely old Skin dry smooth Marked pallor Axillary and pubic hair practically gone Gaping vaginal introitus with perineal scar Cervix and uterus atrophic Anal orifice scarred and contracted

Laboratory data Urine normal RBC 3,130 000 Hgb 10.4 Gm (74%) WBC 5,250 Hematocrit 29% Blood sugar 88 mg % (3 hrs after eating) Total protein 7.5 Gm % Plasma cholesterol 124 mg % Blood sodium 141.5 mEq/l Serum potassium 15.9 mg % Serum phosphorus 4.5 mg % Blood iodine (total) 5.8 micrograms % Glucose tolerance test (blood sugar mg %) fasting specimen 97 $\frac{1}{2}$ hr, 105 2 hrs 86 3 hrs 95 no glycosuria Water test part 1—positive part 2—“A” factor 7.3 (positive) BMR minus 31%

Roentgenographic findings Skull—lateral area of sella measures 74 sq mm Chest negative

Treatment Testosterone 2 pellets (75 mg each) Desoxycorticosterone (DOCA), 2 pellets (75 mg each) Thyroid (desiccated USP), 1 gr daily after 1 month Ferrous sulfate 15 gr daily

Progress notes

WEEKS

6 Appetite has improved Hair starting to grow on pubis RBC 3,510,000 No change in Hgb or WBC Differential polymorphonuclears 54%, lymphocytes 34% monocytes 6%, eosinophils 2%, basophils 2% Patient went into shock while awaiting basal metabolism test Given intravenous glucose and revived BMR minus 3% Admitted to hospital for dilatation of the anal stricture

14 Much better and can go shopping now Hair growing Weight 110 $\frac{1}{4}$ lbs RBC 3,900,000 Hgb 11.4 Gm (82%) Testosterone 2 pellets (75 mg each) desoxycorticosterone 2 pellets (75 mg each) thyroid 1 gr daily Feosol, 15 gr daily

20 Improving Pubic and axillary hair increased Constipated Weight 115 lbs BP 140/110 RBC 3,730,000 Hgb 11.8 Gm (84%) Blood sugar 102 mg % (4 hrs after eating) Plasma cholesterol 136 mg % Roentgenogram of chest—lungs clear heart larger than on previous examination (11.7 cm to 12.3 cm) Additional therapy stilbesterol 0.5 mg orally daily

28 One day of vaginal bleeding Severe sore throat treated successfully with penicillin RBC 3,640,000 Hgb 11.2 Gm (80%) Testosterone 2 pellets (75 mg each) Desoxycorticosterone, 2 pellets (75 mg each) Thyroid, 1 gr daily

40 Vomits occasionally Head pains Fatigued sometimes Slight vaginal flow for 1 day every month with stil

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FIG 51 (*Left top*) SIMMONDS DISEASE — ENLARGEMENT OF SELLA TURCICA (See Protocol 5 VI) Although patient appears to be fairly well nourished there has been weight loss (20 lbs) asthenia decrease in pubic avillary and body hair Cause — pituitary tumor without visual field changes



FIG 53 (*Right top*) SIMMONDS DISEASE (SHEEHAN TYPE) (See Protocol 5 VII Figs 52 54) Note that extreme emaciation is not present after 36 years of marked hypopituitarism



FIG 52 (*Left bottom*) SIMMONDS DISEASE (SHEEHAN TYPE) (See Protocol 5 VII Figs 53 54) Age 61 Onset of disease following severe postpartum hemorrhage at age 31



FIG 54 (*Right bottom*) Hip JOINTS IN SIMMONDS DISEASE (See Protocol 5 VII Figs 52 53) Hypertrophic joint changes may occur in hypopituitarism as well as in hyperpituitarism (acromegaly)



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FIG 57 SIMMONDS DISEASE (See Iro tocol 5 IV Fig 56) Age 43 Normal development until 16 or 17 Sella turcica normal size 67 sq mm Roentgenogram of hands showing bone age of 16 years Two years after therapy radial epiphyses closed

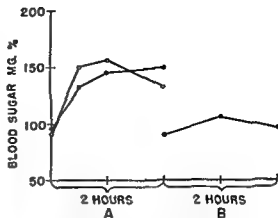


CHART 17 ORAL GLUCOSE TOLERANCE CURVE IV SIMMONDS DISEASE Age 49 female Amenorrhea since age 40 without any vasomotor symptoms Loss of axillary and pubic hair BP 120/10 Urinary hormone assays for FSH and estrin negative, 17 ketosteroids 3 mg/24 hrs Plasma cholesterol 147 mg % BMR minus 17% Desoxycorticosterone acetate and testosterone pellets implanted Plasma cholesterol rose to 357 mg % Given proloid (gr 1/2 orally) with further improvement Plasma cholesterol 200 mg % BP rose to 160/120 later leveled off to 140/100 Regrowth of pubic hair Pellets of desoxycorticosterone (150 mg) and testosterone (150 mg) implanted again after 3 months Still effective 9 months later and no complaints

(A) Glucose tolerance curves before treatment Line with hollow dots shows capillary blood line with solid dots venous blood

(B) Glucose tolerance curve 1 year later The curves are the reverse of what usually occurs A is a diabetic type and B is a low curve typical of hypopituitarism Is this the result of desoxycorticosterone acetate?

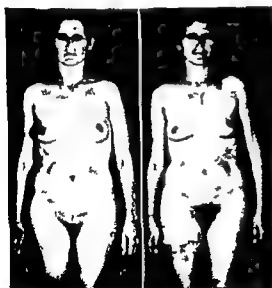


FIG 58 SIMMONDS DISEASE (SHEEHAN TYPE) (See Protocol 5 V) (Left) Two months after initiation of treatment Patient developed Simmonds disease after postpartum hemorrhage She survived rectal surgery after multihormonal therapy A slight amount of pubic hair has grown (Right) Regrowth of pubic hair Patient maintained on thyroid (desiccated USP 1 gr) testosterone and desoxycorticosterone pellets



FIG 55 ANOREXIA NERVOSA (See Protocol 5 VIII)

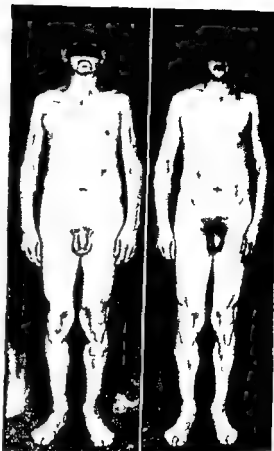


FIG 56 SIMMONDS DISEASE (See Protocol 5 IX Fig 57) Age 43 *Chief complaints* Cessation of growth at 16 years of age Never shaved no voice change moderate libido Married at 35 sexual life unsatisfactory Bone age at 43 16 years (*Left*) Condition before therapy Aspermia before treatment and after 6 months of chorionic hormone average 5 000 to 6 000 units weekly methyltestosterone 10 mg daily and thyroid (desiccated USP) $\frac{1}{2}$ gr daily (*Right*) Condition of patient after 5 months of only methyltestosterone (30 mg daily) Spermatogenesis returned with successful impregnation Total sperm count 50 000 000 Shaves every other day normal sexual function and general improvement Water test positive (Hurxthal L M Bruns H J and Musulin N Development of spermatogenesis in hypogonadism J Clin Endocrinol 2 1245)

	PITUITARY MYXEDEMA (Secondary)	THYROID MYXEDEMA (Primary)
-Potassium	Normal or increased ³	Normal
Chlorides	Normal or decreased ^{1 2 9}	Normal
Function tests		
Glucose tolerance	Normal or increased ^{3 8 10}	Variable
Insulin tolerance	Rapid drop in level slow recovery ^{2 9}	Slow drop faster recovery ^{8 9}
Adrenal water	Positive ^{8 9}	Usually negative unless pituitary secondarily affected and deficient in ACTH (?)
Miscellaneous		
Basal metabolic rate	Low ^{8 10}	Low ³
Electrocardiogram	Normal or few changes ^{3 8}	Low voltage, flat or inverted T waves ³
Gastric analysis	Anacidity ³	May have acid
Urinary hormone assays		
FSH	Negative usually ⁹	Negative or increased after menopause
17 ketosteroids	Absent or very low ^{8 9}	Low ³
Vaginal smears	Estrogen deficient ^{3 8}	May have estrogen effect
D ROENTGENOGRAPHIC FINDING		
Sella turcica	Normal or enlarged ^{1 4 8}	Normal, except in cretinism or aneurysm of internal carotid artery

III TREATMENT

- A HORMONAL (see Fig 59)
 - 1 The following should be used before thyroid is administered
 - a Salt—adequate intake
 - b Desoxycorticosterone acetate (DOCA)

- c Testosterone
- 2 Thyroid (desiccated USP)
 - a Dosage—oral ¼ gr daily initially then increase cautiously
 - b Small doses prevent
 - (1) Adrenal insufficiency
 - (2) Coronary complications

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SECTION 6

PITUITARY MYXEDEMA

I DEFINITION

A condition clinically indistinguishable from primary myxedema (see 25 \III), due to a predominant thyrotropic deficiency of the anterior pituitary (see Protocol 6 \I)^{1 9 11}

II DIAGNOSIS

A COMMENT

- 1 The diagnosis of pituitary myxedema will increase as the number of individuals with idiopathic myxedema are subjected to roentgenograms of the skull
- 2 It is to be admitted that even without enlargement of the sella, a few cases of

idiopathic myxedema may be of pituitary origin

- 3 Tests for adrenal insufficiency are usually normal in primary thyroid myxedema, thus serving as an important differential point
- 4 It is plausible that in primary thyroid myxedema of long standing, the pituitary gland itself may become deficient due to myxedematous changes thus producing a state of panhypopituitarism, in which case tests for gonadotropic thyrotropic and adrenal cortical function would point to a primary pituitary disorder
- 5 The differences between the two types are tabulated below

	PITUITARY MYXEDEMA (Secondary)	THYROID MYXEDEMA (Primary)
B GENERAL		
Occurrence	Rare	More common
Complaints	Same	Same
Headache	Common	Not usual
Deafness	Absent	Occasionally ¹²
Angina pectoris	Not likely to be present	Likely ⁵
Myxedema heart	Reported	Often present
Menorrhagia	Absent	Possible ⁵
Amenorrhea	Usual ⁷	Found in some ⁵
Hypoglycemic shock	May occur ⁵	Absent
Appearance	Identical	Identical
Integument changes	Same	Same
Pigmentation	Absent may have freckles	May be present
Hair	Absent or very little	Decreased may be increased ¹²
Visual fields	Variable	Normal
Blood pressure	Normal or decreased may be elevated before onset ^{1 8}	Normal or elevated ¹²
Sensitivity to thyroid	May be marked and also invoke angina of effort	Absent or occurs very rarely except for invoking angina of effort
C LABORATORY DATA		
Blood chemical analyses		
Nonprotein nitrogen	Normal or rarely increased ⁹	Normal or rarely increased
Protein	Lower than for primary myxedema ^{3 5 8}	Normal or increased ⁵
Cholesterol	Usually increased ⁵	Usually increased ⁵
Sodium	Decreased (maybe) ^{1 3 9}	Normal

SECTION 7

PITUITARY ADRENAL INSUFFICIENCY

(Pituitary Addison's Disease)

I DEFINITION

A condition due to a predominant deficiency of the pituitary adrenotropic hormone and characterized by all the symptoms of true Addison's disease except for the mucous membrane pigmentation and black (ink spot) freckles which are usually seen in the latter (see Protocol 7 VI to VIII)

II DIAGNOSIS

A COMMENT (see Fig 60)

- 1 Pituitary 'Addison's disease' is essentially similar to Simmonds disease
- 2 A comparison of the two conditions is made in the following section

	<i>Pituitary Adrenal Insufficiency</i>	<i>Addison's Disease</i>
B GENERAL		
Complaints	Same	More marked progressive anorexia weakness and weight loss
Diarrhea	Rare	Marked only in acute crisis
Hypoglycemic attacks	Occasionally	Common especially at time of infection
Menses	Amenorrhea usually	Normal
Appearance	Looks sick	Looks sicker
Integument		
Color	No darkening peculiar yellow	Often generalized darkening especially at exposed surfaces
Pigmentation of mucous membranes	Absent	Present usually
Vitiligo	Present	Present
Freckles (black)	Absent	Present
Hair		
Facial	Scant	Normal or decreased
Axillary	Absent	Normal or decreased
Pubic	Absent	Normal or decreased
Body	Scant	Normal
Visual fields	Variable	Normal
Blood pressure	Low, unless previous hypertension	Low unless previous hypertension
Genitalia	Variable findings, usually atrophy	Normal
C LABORATORY DATA		
Urine		
Urea	Normal or decreased	Normal or decreased
Sodium	Increased	Increased
Potassium	Normal	Decreased
Chlorides	Increased	Increased
Hematology		
Red blood cells	Normal or decreased ³	Decreased or increased (crisis)
Hemoglobin	Normal or decreased ³	Normal or increased (crisis)
White blood cells	Normal	Normal or increased (crisis)

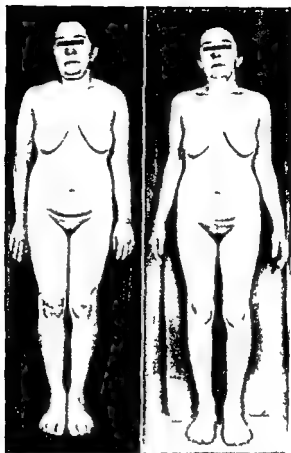


FIG 59 PITUITARY MYXEDEMA AND ADRENAL INSUFFICIENCY (See Protocol 6 \I)
(Left) Before treatment patient appeared to be typically myxedematous but history and loss of pubic and axillary hair raised question of pituitary origin Weight 136 lbs BP 96/80 Plasma cholesterol 309 mg % Electrocardiogram abnormal Adrenal water test positive Sella enlarged *(Right)* Nine months later after continuous therapy with thyroid testosterone and desoxycorticosterone Weight 121 lbs BP 160/100 Much improved Regrowth of axillary and pubic hair

found to have low blood pressure. Com-
plained of weakness and fatigue. About 1½
years before admission began to have spells
of vomiting occurring in the morning and
associated with vague lower abdominal pain.
Noted dryness of her hair and decreased
perspiration. A few months later speech be-
came slow, and voice seemed lower in pitch.
Lost a great deal of her pubic, axillary and
upper lip hair. Anemia discovered. Lost 22
lbs in the past year because of anorexia.
Around 3 months before entry, so weak that
she could not work.

Physical examination. Age 41, female mar-
ried. Weight 136 lbs. Height 61 in. Pulse
60. BP 96/80. Looks pale and pasty. Puffi-
ness around face, eyes, hands, fingers and
toes. Skin = dry, thick. Marked pallor of
palms, nails and mucous membrane. Nails
normal. Axillary hair absent, pubic, very
scanty. Scalp hair is very dry, coarse. Gin-
givitis and pyorrhea. Speech slow and thick.
Pelvic normal. Her movements are usually
slow.

Laboratory data. Urine normal. RBC 3 830
000. Hgb 11.5 Gm (82%). WBC 5 000.
Differential: polymorphonuclears 44%,
lymphocytes 28.5%, monocytes 5%, eos-
inophils 1.5%, basophils 3%. PAH 32 mg
%. Total protein 8.3 Gm %. Albumin
4.4 Gm %. Globulin 3.9 Gm %. A/G
ratio 1.1. Plasma cholesterol 309 mg %.
Glucose tolerance test (blood sugar mg
%) fasting 78 ½ hr 126 2 hrs 113 3
hrs 85. Urinalysis negative for sugar dur-
ing tolerance test. Adrenal water test pos-
itive. Bilirubin 0.2 mg %. Sedimentation
rate 81 mm/hr. EKG delayed AV con-
duction, abnormal T2 and T4. Urinary
hormones: FSH weak positive (uncon-
centrated), 17 ketosteroids 3.6 mg/24 hrs.

Röntgenographic findings. Skull—sella ap-
pears enlarged, measures 140 sq mm, but
the anterior and posterior clinoids are in-
tact. Chest normal.

Treatment. Testosterone 1 pellet (75 mg)
Desoxycorticosterone 1 pellet (75 mg)
Salt to be used liberally. Thyroid (desic-
cated, USP) 1 gr daily 2 weeks later.

Progress and treatment

WEEKS

3. Weight 134 lbs. Pulse 78 to 80. BP

120/85. Patient looks about the same.
Feels warmer. Complains of noises in
head and an occasional headache.
Sleeps poorly. Plasma cholesterol 245
mg %. Urinary hormones: FSH weak
positive (unconcentrated), 17 keto-
steroids 3.6 mg/24 hrs. Thyroid 1½
gr daily.

7. Weight 132½ lbs. Pulse 80. BP
125/84. Pubic and axillary regions
show slight growth of hair. RBC
3,790 000. Hgb 11.2 Gm (80%).
WBC 5 400. Differential: polymorpho-
nuclears 45%, lymphocytes 41%,
monocytes 12%, eosinophils 2%.
Plasma cholesterol 175 mg %. Total
protein 6.7 Gm %. Thyroid 1½ gr
daily.

11. Weight 128 lbs. Pulse 84. BP 120/84.
Improved. No hot flashes. RBC 4 150,
000. Hgb 11.4 Gm (84%). WBC
5 000. Sedimentation rate 59 mm/hr.
Thyroid 1½ gr daily.

20. Feels fine. BP 120/85. Weight 117½
lbs. Thyroid 1½ gr daily. Desoxy-
corticosterone 1 pellet (75 mg). Tes-
tosterone 1 pellet (75 mg).

24. Much stronger. No complaints. Pulse
80. BP 160/100. Weight 119½ lbs.
RBC 4 520 000. Hgb 12.4 Gm (89%).
WBC 5 000. Plasma cholesterol 132
mg %. Thyroid medication continued.
Pellets still present.

48. No complaints. Working. Amenorrhea.
Axillary and pubic hair maintained.
BP 150/100. No pellets. Thyroid 1½
gr daily.

Comment. Myxedema presumably of pitui-
tary origin associated with weakness, ano-
rexia, loss of axillary and pubic hair and
amenorrhea at age of 34 with occurrence of
hot flashes which ceased in 1 year. Low
BMR and high plasma cholesterol. Positive
adrenal water test. Excellent response to
testosterone, desoxycorticosterone and thy-
roid. The finding of weak positive urinary
FSH although decreased for the meno-
pause suggests that thyrotropic and adreno-
corticotrophic hormones were chiefly defi-
cient. In long standing cases of primary
myxedema it is entirely possible that pi-
tuitary deficiency may result.

	<i>Pituitary Adrenal Insufficiency</i>	<i>Addison's Disease</i>
Eosinophils	Increased	Increased ²
Hematocrit	Decreased usually	Decreased or increased with fluid loss
Blood chemical analyses		
Sugar	Normal or decreased	Normal or decreased (crisis)
Nonprotein nitrogen	Normal	Normal or increased (crisis or late in disease)
Protein	Normal ³ or decreased (unless simultaneous pituitary myxedema)	Normal or increased (crisis or late in disease)
Albumin	Decreased	Normal or decreased
Globulins		
Alpha	Decreased	Normal or slightly decreased
Beta	Normal or increased	Normal
Gamma	Normal or increased	Increased
Fibrogen	Normal or increased	Normal or increased
Cholesterol	Normal or decreased ³	Normal or decreased
Sodium	Normal or decreased ³	Normal or decreased (crisis or late in disease)
Potassium	Normal ³	Normal or increased (crisis or late in disease)
Calcium	Normal ³	Normal or decreased (crisis)
Phosphorus	Normal or decreased ³	Normal or increased (crisis)
Chlorides	Decreased	Normal or decreased (crisis or late in disease)
Function tests		
Glucose tolerance	Normal or increased ³	Normal or increased
Insulin tolerance	Decreased very low curve ¹	Decreased, very low curve
Adrenal water	Positive	Positive
Eosinophils	Usually delayed response	No response
Miscellaneous tests		
Basal metabolic rate	Decreased often below minus 20 per cent	Decreased, rarely below minus 20 per cent
Blood volume	Normal	Normal or decreased (crisis or late in disease)
Urinary hormone assays		
FSH	Usually negative	Normal unless malnutrition
17 ketosteroids	Absent or very low (about 0 to 2 mg/24 hrs) ^{1 2}	Absent or very low (about 2 to 4 mg/24 hrs)
D ROENTGENOGRAPHIC FINDING		
Sella turcica	Normal or enlarged	Normal

PITUITARY MYXEDEMA AND ADRENAL INSUFFICIENCY

PROTOCOL VI FIG 59

<i>Family history</i>	Cardiovascular disease and diabetes	<i>History of present illness</i>	Menarche at 14 years of age periods regular but scanty
<i>Past medical</i>	Married 17 years One child		Sudden amenorrhea when 34 years old Hot flashes Always sensitive to cold Anorexia
<i>Chief complaint</i>	Weakness of 2 years' duration		Nearly 2 years before entry patient was

- tract BMR minus 10% EKG essentially inversion of all T waves, rate 80
 Thyroid $\frac{1}{4}$ gr daily Sodium chloride 6 to 8 Gm (capsules) daily Frequent feedings to avoid hypoglycemic attacks
- 5 Intervals of good health and recurrent to collapse During these attacks she had
- 11 anorexia, nausea, vomiting weakness and apathy BP 140 to 70 systolic Thyroid $\frac{1}{4}$ gr daily, increased to $\frac{3}{8}$ gr sometimes Sodium chloride 2 Gm (capsules) daily Precortin $\frac{1}{2}$ to 1 cc subcutaneously every second to fifth day Low-carbohydrate high fat and high protein intake with frequent feedings Multiple vitamin capsules 1 daily
- 36 Returned for checkup Tires rather easily Appetite variable No coma for 3 years No paresthesias Pale looks sick Weight 115 lbs Tongue smooth Dry skin Heart normal few extra systoles P_2 is greater than A Pulse 84 BP 190/100 Neurologic examination normal Optic nerve atrophy on the right left normal Urine—albumin 227 mg % few hyaline casts and WBC Hgb 12.8 Gm (91%) WBC 5700 Blood sugar 72 mg % (4 hrs after eating) NIN 38 mg % Blood urea nitrogen 13 mg % Plasma cholesterol 243 mg % Blood chloride 358 mg % Water test positive—A factor in equal to 6 PSP total 45%

Venous pressure 10 cm Sedimentation rate 44 mm/hr Chest roentgenogram—cardiothoracic measurements 13.4 to 25.6, lungs clear Thyroid, increased to $\frac{3}{4}$ gr in 1 month after blood pressure drops Sodium chloride and precortin discontinued

- 39 Feels much better Less fatigue Does her own housework Color good Skin soft BP 190/90 Pulse 80 Weight 115 lbs Thyroid, $\frac{1}{2}$ gr daily
- 54 Letters received from patient and doctor Can do her housework No complaints Weight 109 lbs Pulse 78 BP 180/130
- 69 Report from doctor saying patient is fine No treatment for 6 to 8 months Very active Flatulence only complaint Weight 110 lbs Hgb 80% Pulse 72 BP 160/110 Thyroid, $\frac{1}{2}$ gr daily

Comment This case illustrates the importance of skull roentgenograms in what may appear to be spontaneous myxedema Blood pressure which is usually normal or low in hypopituitarism was elevated in this case Patient responded very well to treatment, and at present she feels fine by taking only small doses of thyroid The sequence of events is difficult to determine The following conjectures are possible primary myxedema, aneurysm pituitary deficiency, adrenal cortical insufficiency, lowering of blood pressure decrease of pressure in aneurysm increase in adrenocortical function and several other sequences are possible

PITUITARY ADRENAL INSUFFICIENCY

Family history Tuberculosis cancer and cardiovascular disease

Past medical Five pregnancies and 1 miscarriage

Chief complaint Vomiting weakness and fainting spells at stool for 1 year

History of present illness

BEFORE ADMISSION

- 2 years Mild vague headaches otherwise well
- 1 year Pyelitis with dysuria and lower abdominal pains scotoma and slight mental confusion Weakness with defecation and nausea at the

PROTOCOL XIII FIG 60

sight of food Recovered entirely in a few weeks

- 1 month Marked weakness, faintness vomiting spells shortly after eating and occasional hematemesis Constipation flatulence and vague epigastric pains unrelieved by food or vomiting Admitted to the hospital for study

Physical examination Age 70 female married Apathetic, dehydrated and evident weight loss but not cachectic Talks slowly at times is disoriented and aphasic Skin very dry, loose, pale and somewhat lemon

PITUITARY MYXEDEMA AND ADRENAL INSUFFICIENCY

PROTOCOL XII

Family history Essentially negative*Past medical* Married 25 years Husband living and well Five children, all normal deliveries Youngest child 14 years old

YEARS BEFORE

ADMISSION

12 Cholecystectomy All teeth were removed D & C for menorrhagia Pathologic report hypertrophic endometritis

10 Diagnosis of hypothyroidism and secondary anemia

5 Permanent loss of sight in right eye after abscess of right maxillary sinus

Chief complaints Weakness, cold hands and feet for 10 years dry, thickened skin and amenorrhea for 12 years*History of present illness* Well and robust until 12 years previously, when she lost about 42 lbs Amenorrhea followed D & C Noticed absent body and scant axillary hair Nails brittle Skin dry and flaky Mentally and physically sluggish Disliked cold weather Hearing impaired Ten years before, BMR was minus 19%, remained low in spite of thyroid medication For some years, endurance and strength very poor Dyspnea, palpitation and fatigue on slight exertion Speech slow and deliberate Stomach easily upset Spells of nausea and vomiting occasionally Constipation about a year Paresthesias and coldness of her hands and feet Admitted to hospital for study*Physical examination* Age 45 female Weight 170½ lbs Height 65½ in Pulse 92 BP 165/110 Temperature 97.6° Typical appearance of myxedema Skin—pale thick, dry, scaly Extremities very cold Nails brittle Hair dry and sparse Axillary and pubic hair scant Body hair absent Paresis of right internal rectus right eye turns out and downward Right pupil is larger than the left Fundi—primary optic atrophy, retinal vessels show marked degree of sclerosis Visual fields—almost total blindness in right eye Patient can count fingers at 1 ft distance in the upper temporal field Left eye 6/6 Thyroid gland slightly enlarged and nodular Heart normal, beats forceful Lungs clear Pelvic normal Reflexes sluggish Speech slow and deliberate*Laboratory data* Urine—1 plus albumin, 40 to 50 WBC per high powered field RBC 4,310,000 Hgb 12.2 Gm (87%) WBC 4,650 Hematocrit 35% NPN 30 mg % Plasma cholesterol 408 mg % Spinal fluid dynamics and analysis normal BMR minus 35% Sedimentation rate 61 mm/hr EKG low voltage and flat T waves Gastric analysis—75° of free acid, 30 min 70°, 45 min*Roentgenographic findings* Skull—a large aneurysm of the right internal carotid artery involving the sella, partially calcified (See Fig 26) Chest—heart slightly enlarged in all its diameters lung fields clear*Treatment* Thyroid (desiccated, USP) ½ gr daily, increased to 1 gr Sodium chloride, 5 to 6 Gm (capsules) daily Feosol 2 tablets t i d Vitamin B complex 2 teaspoonfuls t i d Haliver oil, 1 capsule daily*Diagnoses* Pituitary myxedema and adrenal insufficiency third nerve palsy due to pressure of aneurysm on hypophysis and third nerve*Progress and treatment*

MONTHS

4 Well for 1 month only She suddenly became nauseated and within a few hours was comatose Regained consciousness in 3 or 4 days Given glucose and salt solution rectally at home Second admission to hospital for further study and management Urine normal RBC 4,420,000 Hgb 80% WBC 6,660 Differential polymorphonuclears 52%, lymphocytes 36%, monocytes 8%, eosinophils 2%, basophils 2% NPN 19 mg % Glucose tolerance test (blood sugar mg %) fasting, 70, ½ hr, 90 1 hr 70 2 hrs, 80 3 hrs 70 4 hrs, 60 5 hrs, 40 6 hrs 44 Salt deprivation test unsuccessful because patient became nauseated at the end of the 36th hr Blood chloride had fallen from 523 to 463 mg % during the preceding 8 hrs Blood sugar 50 mg % Prompt recovery with the use of intravenous glucose, saline and adrenal cortical ex

tumor was not considered until later. This patient illustrates the importance of roentgenographic films of the skull in all cases of adrenal insufficiency and hypoglycemic shock, particularly where the usual and characteristic pigmentation of Addison's

disease is not present. She did very well in spite of unavailability of desoxycorticosterone, recurrent episodes of shock and adrenal insufficiency showing that a patient may live comfortably over a period of years with adequate therapy.

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- 2 Hurxthal L M. Unpublished data.
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FIG. 60. PITUITARY ADRENAL INSUFFICIENCY (See Protocol 7 XIII). Adrenal insufficiency with recurrent hypoglycemia due to a chromophobe pituitary adenoma. Patient died at 75 years of age from what seemed to be an acute coronary infarction but this was not verified at autopsy. Generalized arteriosclerosis. No characteristic pigmentation of Addison's disease. Note normal and healthy appearance of patient.

tinged Tongue normal Apical systolic murmur Pulse 64 BP 90/70 Uterus atrophic Arm and knee jerks absent Fundi—Grade 2 sclerosis

Laboratory data RBC 3,180,000 Hgb 65 to 73% WBC 5,200 to 9,200 Reticulocyte count 0.7 to 1% Blood sugar 64 to 148 mg % NPN 24 mg % Plasma cholesterol 156 mg % Carbon dioxide combining power 49 volumes % BMR minus 24%

Progress Profound prostration, marked hypotension and hypoglycemic attacks during her hospitalization Attacks consisted of complete loss of consciousness, followed by partial recovery and then profound sleep with stertorous breathing At times she seemed mentally dull and stuporous Vomited at irregular intervals A mild urinary infection developed A diagnosis of adrenal insufficiency, secondary anemia and pyelonephritis was made Weight 110½ lbs Patient gradually improved with therapy

Treatment Intravenous fluids 10% glucose and saline Adrenalin ½ cc every 3 hrs, as necessary Eschatin 30 cc given for 17 days Sodium chloride 6 Gm (capsules) daily Liver extract (Lilly's concentrated) 7½ cc (intramuscular) Pyridium 1 tablet tid

Second hospital admission One year later Well except for occasional attacks of weakness and vomiting Recurrence of pyelitis and joint pains Admitted in profound shock markedly lethargic and responded very slowly to any questioning BP 68/50 Diagnosis—adrenal crisis With similar therapy given previously she improved daily BP reached 138/78

Next four years At times seemed quite well Appetite was good BP varied anywhere from 128 to 195 systolic However frequent similar spells of weakness collapse and unconsciousness occurred Nausea vomiting and marked anorexia were recurrent Pyelitis and joint pains too Treated at home with salt and eschatin in insufficient dosage

Third hospital admission About 4 years after first admission Admitted to the hospital in acute adrenal insufficiency Frequent bouts of nausea and vomiting Often mentally confused Gingivitis and pyelitis developed Improved slowly with previous

hospital regime Patient looked weak and lethargic Fundi—temporal pallor Skin smooth, scaly and shallow Axillary and pubic hair scant and fine Heart sounds faint BP 150/70 on admission Abdomen distended Knee joints tender, no swelling BMR minus 17 and 20% Postero-graphic film of skull—marked ballooning of the sella with practically complete destruction of posterior clinoids The depth of the sella is approximately 3 cm, left anterior clinoids show some erosion into the tuberculum Pineal gland shows no displacement by measurement Diagnosis—pituitary chromophobe adenoma

Fourth hospital admission Two months after third admission At intervals patient seemed well, however attacks of weakness, accompanied with nausea and vomiting mental confusion pallor, and loss of pulse would recur Painful knees often Patient was maintained on variable doses of adrenal cortical extract and responded fairly well On admission complained of weakness dry mouth, precordial pain and dyspnea Symptoms were such that they indicated a possible coronary occlusion BP 160/70 and 102/78 Urine normal RBC 3,760,000 Hgb 65% WBC 4,550 Blood sugar 128 mg % NPN 21 mg % Total protein 7.7 Gm % Blood chloride 553 mg % Serum sodium 122.3 to 147.4 mEq/l Serum potassium 8.8 to 17.8 mg % (day before death) EKG normal rhythm, low voltage QRS slurred all T waves low or flat Patient suddenly became worse and died Diagnosis—pituitary adenoma, with adrenal insufficiency and secondary pituitary cachexia

Postmortem findings Anatomic diagnoses Pituitary adenoma Adrenal cortical atrophy Bilateral hydrothorax Miliary tuberculosis of lungs (healed) Ascites Moderate generalized arteriosclerosis Leiomyoma of uterus Chronic thyroiditis

Microscopic diagnoses confirmed the gross anatomic findings Chromophobe adenoma of pituitary Atrophy of adrenals Chronic thyroiditis Miliary tuberculosis of the lungs (healed)

Comment Initially adrenal insufficiency was recognized but the possibility of pituitary

j Chlorides	Normal or increased ^{18 22 77 40 60 77 78 83 82 110 111 117}
k Iodine	Normal or increased ¹²
l Magnesium	Normal ²²
m Uric acid	Normal
II HEMATOLOGY	
1 Red blood cells	Normal or increased occasionally decreased
2 Hemoglobin	Normal or increased occasionally decreased
3 White blood cells	Normal
4 Differential	Normal
5 Hematocrit	Normal (blood may show slight dilution without treatment) ^{15 17 117}
C BLOOD CHEMICAL ANALYSES	
1 Sugar	Normal ^{7 15 17 77 61 73 79 87 110 111 113 117}
2 Nonprotein nitrogen	Normal ^{17 19 79 87 117 120}
a Urea nitrogen	Normal ^{7 80 113 116 117 170}
3 Protein	Normal ^{17 19 25 93 104 110 111}
■ Total	Normal
b Albumin	Normal
c Globulin	Normal
d A/G ratio	Normal
4 Uric acid	Normal ^{84 117 170}
5 Cholesterol	Normal ^{17 18 73}
6 Sodium	Normal usually may be increased or decreased ^{19 79 110}
7 Potassium	Normal ^{25 73}
8 Calcium	Normal rarely increased ^{17 97 104 116 170}
9 Phosphorus	Normal ^{17 17 97 108 116}
10 Chlorides	Normal usually may be increased or decreased ^{2, 16 17 170 70 75 80 104 110 111 120}
11 Iodine	Low normal (relation of inorganic to organic is normal) ¹⁷
12 Phosphatase	Normal
13 Creatinine	Normal ^{2 117}
14 Creatine	Normal
15 Total lipids	Normal ⁷³
16 Carbon dioxide combining power	Normal ¹¹⁷
D FUNCTION TESTS	
1 Tolerance	
a Glucose	Normal or occasionally diabetic curve ^{2 7 13 18 74 45 54 60 73 108 116 170}
b Glucose insulin	No data
c Insulin	No data
d Iodine	Normal or low ¹
2 Adrenal water	Normal ⁸³
3 Salt deprivation	Normal ⁷³
4 Balance	
a Nitrogen	Normal ^{70 117}
b Calcium	No data
5 Renal	
■ Phenolsulfonphthalein	Normal ^{17 15 79 116 120}
b Clearance	
(1) Urea	Normal ^{17 21 61}
(2) Creatinine	Normal ¹⁷⁰
(3) Inulin	Normal or decreased ^{180 17}

SECTION ■

DIABETES INSIPIDUS

I DEFINITION	A disease characterized by polyuria, with a urine of very low specific gravity and polydipsia without glycosuria, the disorder may be persistent or characterized by relapses and remissions
II APPEARANCE	Normal or thin, unless complications or associated diseases
III AGE	Average 21 ⁶³ usually occurs before 10, rarely after 50 (incidence 16.5 per 100,000 capita ^{40 87})
IV SEX	Ratio, male to female 2 : 1
V MENTAL DEVIATIONS	Normal, occasionally intelligence lower than average
VI PHYSICAL STATUS	
A NUTRITION	Variable
B HEIGHT	Normal or decreased
C EXTREMITIES	Normal, feet may be edematous late in disease
D SPINE	Normal
E INTEGUMENT	Generally dry temperature may be subnormal
F HEAD	Throat may be dry fundi are normal, unless associated with an intracranial lesion
G NECK	Thyroid normal or colloid goiter may be found
H CHEST	Normal
I HEART AND PERIPHERAL VESSELS	Normal variations
J BREASTS	Normal
K ABDOMEN	Normal
L GENITALIA	Normal
M NEUROMUSCULAR	Normal tremor may be present or absent and reflexes variable depending on etiology
N SPEECH	Normal
VII LABORATORY DATA	
A URINE	
1 General	Large quantities, 5 to 20 liters or more/24 hrs, specific gravity very low—1.001 to 1.005
2 Special analyses	
a Sugar	Absent
b Albumin	Absent later may show slight amount
c Nitrogen	Normal ⁶⁵
d Creatinine	Normal ²²
e Creatinine	Normal
f Sodium	Normal
g Potassium	Normal
h Calcium	Normal ²²
i Phosphorus	Normal

- 4 Traumatic^{9 10 11 47 91 122}
- 5 Postoperative—craniotomy
- 6 Hand Schuller Christian's disease^{60 91}
- 7 Laurence Moon Biedl syndrome

II FAMILIAL TENDENCY^{11 41 60 73}

X PATHOLOGY

A GROSS

- 1 Idiopathic group
 - a Kidneys
 - (1) Enlarged
 - (2) Congested
 - b Ureters—dilated
 - c Bladder—hypertrophy
 - d Heart—normal
- 2 Secondary group
 - a Findings as above
 - b Dependent on basic etiology

B MICROSCOPIC³⁶

- 1 Pituitary
 - a Pars anterior
 - (1) Normal
 - (2) Hyperplasia
 - (3) Cellular destruction
 - b Pars intermedia
 - (1) Normal
 - (2) Hyperplasia
 - c Pars nervosa
 - (1) Normal
 - (2) Colloid—increased
 - (3) Hyaline—increased
- 2 Thyroid
 - a Normal
 - b Hyperplasia with hyperthyroidism
(see Protocol 8 XIV)

XI PATHOLOGIC PHYSIOLOGY

A TYPES OF DIABETES INSIPIDUS

- 1 Persistent—all symptoms remain permanently
- 2 Intermittent⁴⁹
 - a Symptoms may appear and disappear at irregular intervals
 - b During active stage serum contains substance that will inhibit antidiuretic action of posterior lobe extract
 - c During remission serum contains an excess of antidiuretic factor similar to effect of pitressin

B FACTORS INVOLVED

- 1 Deficient secretion of antidiuretic hormone is due essentially to hypofunction of posterior pituitary^{6 78 44}

- 2 If the anterior pituitary lobe's diuretic hormone cannot counterbalance the antidiuretic hormone of the posterior lobe then diabetes insipidus may develop

3 Occurrence of the disease only if

- a Functions of pars neuralis are severely damaged—at least over half must be nonfunctioning^{78 114}
- b Pars glandularis is active^{38 87 114}
- c There is injury of^{39 57 68}
 - (1) Suprapituitary hypophyseal tract
 - (2) Nerve centers at hypothalamic region
- d Adjacent lesions cause pressure on above areas
- e Patient has no serious disorder of
 - (1) Heart
 - (2) Kidneys
- f Thyroid gland is intact³⁹
 - (1) It is questionable that TSH is the diuretic principle of anterior pituitary
 - (2) Diuretic action of anterior pituitary is not mediated through thyroid alone

C PHYSIOLOGIC EFFECTS¹

- 1 Disturbance of exchange of salt and water in the
 - a Tissues
 - b Blood
- 2 Inability of the kidney tubules to reabsorb water in normal quantity^{1 38 91}
 - a Hormonal effect essentially and not nervous mechanism
 - b Plasma sodium chloride may be increased because of this
- 3 Specific gravity of blood increases, if dehydration is present³⁵

XII SYMPTOMATOLOGY

A ONSET

- 1 Sudden after
 - a Injury
 - b Shock
 - c Infectious disease
- 2 Gradual—more common

B GENERAL

- 1 Polydipsia
- 2 Anorexia
- 3 Weight loss
- 4 Constipation
- 5 Polyuria

E MISCELLANEOUS TESTS

- | | |
|--------------------------------------|--|
| 1 Basal metabolic rate | Normal or decreased ^{17 18 73 10 11} |
| 2 Circulation time | Normal ¹⁸ |
| 3 Sedimentation rate | Normal |
| 4 Specific dynamic action of protein | No data, normal probably |
| 5 Gastric analysis | Normal, or higher degree of acidity greater volume of gastric juice, increased pepsin and renin ^{14 19} |
| 6 Electrocardiogram | Normal ⁷³ |
| 7 Blood volume | Normal ^{18 117} |
| 8 pH | No data |
| 9 Spinal fluid | Normal dynamics and content ^{18 19 9 110 10} |
| 10 Electroencephalogram | Normal or abnormal |
| 11 Venous pressure | Normal ¹⁸ |

F URINARY HORMONE ASSAYS

- | | |
|-----------------|---------------------|
| 17 ketosteroids | Normal ⁴ |
|-----------------|---------------------|

G BIOPSY

- | | |
|---------------|--------|
| 1 Endometrial | Normal |
| 2 Testicular | Normal |

H VAGINAL SMEAR

Normal probably

I SEMEN ANALYSIS

Normal probably

VIII ROENTGENOGRAPHIC FINDINGS

A SKULL

- | | |
|-----------------|---------------------|
| 1 Cranial vault | Normal unless tumor |
| 2 Sella turcica | Normal size |
| 3 Sinuses | Normal |
| 4 Mandible | Normal |
| 5 Teeth | Normal |

B EPIPHYSEAL STATUS (bone age) Normal or retarded⁶

C LONG BONES Normal

D VERTEBRAE Normal

E BONE TEXTURE Normal

F MISCELLANEOUS

- | | |
|-------------------|--------|
| Gastro intestinal | Normal |
|-------------------|--------|

IX ETIOLOGY^{11 36 63 86 116}

A BASIC FACTOR—Any lesion which produces a decreased formation and/or obstruction of posterior lobe secretions (see 88 VIII E)

B IDIOPATHIC (PRIMARY)^{15 17 19 93 12}

C SYMPTOMATIC (SECONDARY)

- | |
|--|
| 1 Tumors—(other lesions, i.e., cysts, primary or secondary carcinoma) ^{3 79 15} |
| 19 31 43 49 67 90 98 109 111 |

- | |
|------------------------------|
| a Pituitary gland |
| b Hypothalamus ⁹⁸ |
| c Midbrain |

d Third ventricle

e Pinealoma^{61 70 100}2 Postinfectious^{9 17 19 80 42 111 64 7 73}
76 84 119 10

a Chronic encephalitis (epidemic post vaccinal, etc.)

b Syphilis^{5 19 22 111 91 114 117 10}c Tuberculosis^{58 114}

d Scarlet fever

e Measles⁵⁴

f Influenza

g Metastatic abscesses^{116 123}

h Rheumatic fever

3 Cerebral vascular

- 4 Traumatic^{29 31 37 31 100}
- 5 Postoperative—craniotomy
- 6 Hand Schuller Christian's disease^{33 34}
- 7 Laurence Moon Riedl syndrome

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 - (2) Nerve centers at hypothalamic region
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 - b Blood
- 2 Inability of the kidney tubules to reabsorb water in normal quantity^{1 28 34}
 - a Hormonal effect essentially and not nervous mechanism
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- 3 Specific gravity of blood increases if dehydration is present²⁵

XII SYMPTOMATOLOGY

A ONSET

- 1 Sudden after
 - a Injury
 - b Shock
 - c Infectious disease
- 2 Gradual—more common

B GENERAL

- 1 Polydipsia
- 2 Anorexia
- 3 Weight loss
- 4 Constipation
- 5 Polyuria

- 6 Impotence
- 7 Weakness
- 8 Headache
- 9 Vision
 - a Blurred sometimes
 - b Transient hemianopsia is common (syphilitic cases)
- C MARKED RESTRICTION OF FLUID INTAKE PRODUCES
 - 1 Cramps in
 - a Abdomen
 - b Legs
 - 2 Nausea
 - 3 Vomiting
 - 4 Diarrhea
 - 5 Weight loss
 - 6 Tachycardia
 - 7 Headache (may be intense)
 - 8 Faintness
 - 9 Exhaustion
 - 10 Sweating
 - 11 Hypothermia
 - 12 Psychic disturbances
 - 13 Collapse

XIII DIAGNOSIS

- A URINARY FINDINGS
 - 1 Daily output enormous, ranging from 5 to 50 liters
 - 2 Specific gravity is usually less than 1.010
 - a In a 24 hr urine specimen
 - b After refraining from fluids as long as possible (see 2 VIII E 1 c) ⁹
 - 3 Glycosuria is absent
 - 4 Salt loading test (see 2 VIII E 1 a) ⁴
 - a Urinary output is increased
 - b Inability to concentrate salt in urine
 - 5 Salt restriction—see 2 VIII E 1 b ^{7 11 73}
- B THIRST EXCESSIVE

XIV DIFFERENTIAL DIAGNOSIS

- A DIABETES MELLITUS
 - 1 Association with diabetes insipidus is rare ^{7 9 50 80 107 108 120}
 - 2 Urine
 - a Specific gravity—high
 - b Sugar present
 - 3 Sugar (blood)—elevated
 - 4 Glucose tolerance—decreased
- B HYPERPARATHYROIDISM (see 38 VIII)
 - 1 Calciuria in excess

- 2 Phosphorus (serum)—decreased
- 3 Calcium (serum)—increased
- C FUNCTIONAL POLYURIA
 - 1 Habit of drinking excessive amounts of fluids
 - 2 Enormous intake of fluids can be restricted without discomfort, specific gravity of urine will be over 1.010
 - 3 Kidneys can concentrate chlorides
 - 4 Symptoms are transient
 - 5 Evidence of a psychiatric condition may be noted
 - 6 Pitressin effects, if any, are limited
 - 7 Adrenal water test—negative
- D CHRONIC NEPHRITIS
 - 1 Urine contains
 - a Albumin
 - b Casts
 - 2 Renal function decreased
 - 3 Associated cardiovascular disease may be found

XV COMPLICATIONS SEQUELAE AND ASSOCIATED DISEASES

- A DIABETES MELLITUS—Both diseases may occur together, but rarely ^{7 9 50 80 107 108 120}
- B HAND SCHULLER CHRISTIAN'S SYNDROME—see 92 V E 4
- C LAURENCE MOON BIEDL SYNDROME—see 95
- D HYPERTHYROIDISM—see Protocol 8 IV ^{71 73}

XVI TREATMENT

- A GENERAL MANAGEMENT
 - 1 Diet
 - a Low salt intake may be helpful to decrease urinary
 - (1) Volume
 - (2) Chloride concentration
 - b Protein foods in large amounts have been suggested
 - 2 No attempt should be made to reduce fluid intake
 - 3 Syphilitic treatment if indicated
 - 4 Lumbar puncture—cures have been reported following this procedure possibly due to lowered pressure of cerebrospinal fluid—^{46 59 107}
 - 5 Thyroid ablation ^{1 27 34 71 111 112}
 - a Reduction sometimes in
 - (1) Polyuria
 - (2) Iodine excretion

- b Subsequent myxedema is treated with desiccated thyroid
- c Value questionable as a universal procedure
- 6 Diuretics may relieve some symptoms
- 7 Surgical—see 13 VII¹⁰

II ROENTGEN¹⁰ 106 11

- 1 Indicated in the following
 - a Neoplasms of pituitary and surrounding areas
 - b Hand Schuller Christian's disease
- 2 Results may be satisfactory

C HORMONAL

- 1 Pituitrin (specific)
 - a Preparations
 - (1) Powder used as snuff or by in-sufflation¹⁰
 - (a) Dosage—by trial and error average 2 to 3 times a day¹⁰
 - (b) Contraindication — allergy to powder¹⁰
 - (2) Suspension in oil—intramuscular¹⁰ 63 80 122
 - (a) One cc. containing 5 pressor units may relieve symptoms for 10 to 82 hrs
 - (b) 0.25 to 0.30 cc. can be used in daily doses but often followed by reactions (see below)¹⁰
 - (3) Pellets—unsatisfactory because of local and/or general reactions¹⁰
- b Results
 - (1) Antidiuretic effect (kidney threshold for excretion of water raised)
 - (2) Specific gravity of urine increased
 - (3) Water balance becomes positive
 - (4) Urinary excretion of the following is decreased
 - (a) Nitrogen
 - (b) Chlorides (unchanged some times)
 - (5) Relative decrease of
 - (a) Total nitrogen
 - (b) Sodium chloride of plasma
 - (6) Slight increase in plasma volume
 - (7) Chlorides (serum) become normal
 - (8) Thirst less severe

- c Effects of overdosage
 - (1) Oliguria
 - (2) Water retention
 - (3) Weight gain may be rapid
 - (4) Headache
 - (5) Restlessness
 - (6) Drowsiness
 - (7) Fainting
 - (8) Weakness
 - (9) Pallor
 - (10) Menstrual flow may be increased in
 - (a) Amount
 - (b) Duration

D MISCELLANEOUS

- 1 Comment—the following medications are of variable and questionable value
- 2 List
 - a Antuitrin 'S'¹
 - b Intermediate lobe preparations¹⁰
 - c Thyroid (desiccated U.S.P.)
 - d Desoxycorticosterone¹⁰
 - e Testosterone (if an associated testicular deficiency is present)¹⁰
 - f Estrogens¹⁰ 104
 - g Amudopyrine¹⁰ 67 73 104

XVII PROGNOSIS

- A IDIOPATHIC
 - 1 Long life usually, 50 years average
 - 2 Spontaneous cessation or remissions in some
- B SYMPTOMATIC
 - 1 Outcome depends on pathologic lesion
 - 2 Fatality may come early
- C PREGNANT PATIENT¹ 10 13 23 28 30 33 34 74 97 113
 - 1 Symptoms may
 - a Increase
 - b Improve
 - c Remain unaltered
 - d Develop in any stage
 - 2 Outcome as for others without complications

XVIII CAUSES OF DEATH

- A ALCOHOLISM
- B PNEUMONIA
- C PRIMARY LESION
- D COMA

DIABETES INSIPIDUS AND PRIMARY HYPERTHYROIDISM

Protocol XIV

Family history Cardiovascular disease*Past medical* Pneumonia and hives*Chief complaints* Weight loss for 5 months and excessive thirst*History of present illness* Fractured skull 4 years ago, resulting in polydipsia and polyuria Voided almost every hour night and day Five months before admission noted tremor and decrease in weight, a total loss of 30 lbs*Physical examination* Age 40, male Weight 137½ lbs Height 66¼ in Pulse 126 BP 150/80 Very toxic Tremor Thyroid slightly enlarged and firm*Laboratory data* Specific gravity of urine after 9 hrs without fluids 1.002 Total output 7 quarts/24 hrs BMR plus 70%*Treatment and progress* Nasal insufflations with pituitary powder relieved the poly-

dipsia and polyuria Gradual reduction of BMR to minus 7% in 2 months with methylthiouracil Gained 18 lbs Subtotal thyroidectomy Condition 6 months later, BMR plus 10% Weight 144 lbs Pulse 68 No trouble with thirst, except when over heated

Comment There was no decrease in diabetic insipidus symptoms for 4 years after skull fracture Hyperthyroidism probably began with onset of weight loss The effectiveness of insufflation of pituitary powder which was given simultaneously with methylthiouracil does not permit evaluation of role played by the latter drug In any event a "cure" of both disorders was accomplished by methylthiouracil and a subtotal thyroidectomy

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SECTION 9

GIGANTISM

I DEFINITION	Gigantism is characterized by a prepuberal hyperfunction of the pituitary growth hormone cells, causing height and rate of growth beyond normal age limits (see Fig 61)
II APPEARANCE	Strikingly and abnormally tall with slouchy posture otherwise normal during active stage of the disorder
III AGE	Usually begins in childhood or infancy if great height is reached, ⁴ or may develop during puberty, causing acromegalic gigantism (see below), may follow period of relative dwarfism ³⁴
IV SEX	Majority in males ²⁵ 77
V MENTAL DEVIATIONS	
A INTELLIGENCE	Variable may be feeble minded ⁷⁷
B RESPONSIVENESS	Normal or subnormal
C OTHER ABNORMALITIES	Moody, irascible may become psychotic
VI PHYSICAL STATUS	
A NUTRITION	Normal
1 Weight	Proportionate to height
2 Fat distribution	As in prepuberal habitus, rarely obese in active stage of growth
B HEIGHT	Final height depends on age of onset, duration and degree of pituitary activity (excluding presence of back deformity) may reach 108 in or more ^{8 20 40} abnormal rate of growth may be punctuated by periods of retarded growth (see Charts 18 to 21) ³⁰
C EXTREMITIES	
1 Upper	Proportionate but may become eunuchoid later
a Hands	Large
b Fingers	Proportionate but may become eunuchoid rarely arachnodactyly ⁴⁵
c Span	Normal or may become greater than height
2 Lower	As for upper bony deformity around joints often genu valgum
■ Feet	Proportionate may swell
b Toes	Exostoses and deformities may develop bunions and hammer toes from small shoes rarely arachnodactyly ⁴⁵
D SPINE	Round back early, later marked kyphosis and scoliosis may occur from osteoporosis
E INTEGUMENT	
1 General	Normal or fine and soft if no sexual development
a Texture	Often subnormal ⁸
b Temperature	Normal or excess
c Moisture	

d Eruptions	Not common
e Pigmentation	Cafe au lait type circumscribed, freckles
f Color	Normal or sallow when pituitary becomes hypoadrenal
2 Hair	
a Head	Normal or luxuriant and coarse
b Facial	Depends on state of sexual development, usually slight amount
c Axillary	Depends on state of adrenal and gonadal activity (see 96 IV E) may be absent
d Pubic	As axillary may have female escutcheon
e Body	May be increased if onset late in puberty, ¹⁷ or falls out later when hypofunction ensues
F HEAD	
1 Shape and size	Proportionate or slight brachycephaly (exceptions see Protocol 9 XVI) occasionally small leontiasis ossea facial hypertrophy ⁶
2 Facial expression	Normal or rather serious
3 Eyes	
a General	Normal exophthalmos rarely present with or without hyperthyroidism ^{28 24 1}
b Fundi	Normal papilledema or pallor of optic heads
c Visual	
(1) Fields	May be reduced bilateral hemianopsia possible
(2) Acuity	Normal or decreased
4 Ears and nose	Normal impaired sense of smell or anosmia deafness in some cases lobule may be absent (see Protocol 9 XV)
5 Mouth and throat	
a General	Normal or enlarged tongue
b Teeth	Normal or big
c Larynx (voice)	Proportionate to sexual development may be low if partially acromegalic
G NECK	
1 General	Normal or thin * Adam's apple prominent
2 Thyroid	Normal or increased in size
H CHEST	Proportionate except late in disease may be funnel or pigeon type ¹⁷
I HEART AND PERIPHERAL VESSELS	
1 Heart	Normal
2 Rate and rhythm	Normal or slow regular
3 Blood pressure	Normal to hypertensive diastolic is variable lower if hyperthyroidism is present
4 Peripheral arteries and veins	Normal
5 Vasomotor	See integument E 1
J BREASTS	
1 Male	May show colostrum ²⁴ occasionally pendulous
2 Female	Poorly developed
K ABDOMEN	
1 Liver	May be increased proportionately to general size
2 Spleen	Findings as for liver
3 Hernia	May be present
4 Tumor	None found

L GENITALIA

1 Male

a Penis

Normal, hypoplastic or proportionately enlarged, depending on age of onset (see Protocols 9 \V and \VII)

b Testes

As above (1a)

c Prostate

As above (1a)

2 Female

a External

As above (1a)

b Internal

As above (1a)

M NEUROMUSCULAR

1 Muscles

During active hypersecretory stage, may be unusually powerful but often easily fatigued

2 Gait

Leisurely, may be hampered by poor foot mechanics

3 Body movements

Handicapped by bulk, rare exceptions

4 Tremor

None, may be found if active hyperthyroidism is present

5 Paresthesias

None or may be observed if there is local extension of tumor

6 Reflexes

Normal unless extrasellar extension of tumor²³

N SPEECH

Normal but not lively

VII LABORATORY DATA

A URINE

1 General

Normal

2 Special analyses

a Sugar

May be found

b Creatine

Increased probably

c Creatinine

Increased probably

d Iodine

No data increased if thyroid hyperactivity present

B HEMATOLOGY

1 Red blood cells

Normal or low^{7 14 1}

2 Hemoglobin

Variable

3 White blood cells

Normal⁷

4 Differential

Normal^{7 14}

C BLOOD CHEMICAL ANALYSES

1 Sugar

Normal during growth period later may increase

2 Nonprotein nitrogen

Normal or below average^{7 21}

3 Protein

Normal⁷

4 Uric acid

Normal

5 Cholesterol

Variable, below average with pituitary overactivity⁵ when diabetes present may be increased^{14 1}

6 Sodium

Normal

7 Potassium

Normal

8 Calcium

Normal

9 Phosphorus

No data presumably marked increase (6 to 7 mg %) based on findings in active acromegaly or acromegalic gigantism^{7 23}

10 Phosphatase

No data but should be increased in active state

11 Chlorides

Normal probably or low¹⁴

12 Iodine

No data should be increased especially if overactive thyroid function

13 Creatine

No data could be increased as in acromegaly

14 Creatinine

Increased

D FUNCTION TESTS

- 1 Tolerance
 - a Glucose Normal probably except when adulthood is reached (see Protocol 9 \V)^{7 14 1}
 - b Glucose insulin No data
 - c Insulin No data
 - d Iodine No data increased if hyperactivity of thyroid is present
- 2 Adrenal water Normal unless pituitary becomes inactive¹
- 3 Salt deprivation No data normal possibly or abnormal in burnt out cases
- 4 Balance
 - a Nitrogen No data positive in active stage
 - b Calcium No data negative possibly as in acromegaly

F MISCELLANEOUS TESTS

- 1 Basal metabolic rate Variable^{11 1}
- 2 Circulation time No data presumably normal unless elevated basal metabolic rate
- 3 Sedimentation rate Normal
- 4 Specific dynamic action of protein Normal or increased¹
- 5 Electrocardiogram Normal

F URINARY HORMONE ASSAYS (see Acromegaly, 10 VII F)

- 1 FSH Variable (see Protocol 9 \V)¹
- 2 LH Not present
- 3 Estrogens No data
- 4 Pregnanediol No data
- 5 17 ketosteroids Very low corresponding to gonadal and adrenal activity (see Protocol 9 \V)²¹
- 6 11 oxysteroids No data
- 7 Aschheim Zondek Negative²⁴
- 8 TSH No data

G Biopsy

- 1 Endometrial Should be hypoplastic but depends on sexual development
- 2 Testicular See microscopic pathology

H VAGINAL SMEAR

Estrogen effect reported²⁰

I SEMEN ANALYSIS

Normal or decreased count

VIII ROENTGENOGRAPHIC FINDINGS

A SKULL

- 1 Cranial vault Proportionately thickened or greatly increased occasionally open sutures hyperostoses (see Protocol 9 \VI),⁶ exostoses (see Figs 66 67 and 70)¹
- 2 Sella turcica Normal rarely^{8 20 45} enlarged in most cases may decrease with roentgen therapy (see 2 \IV for measurements and Protocol 9 \V)²¹
- 3 Mandible Proportionate increase in size except late in disease
- 4 Sinuses Enlarged particularly frontals may be narrow
- 5 Teeth Normal or perhaps enlarged

II EPIPHYSEAL STATUS (bone age)

Retarded often by several years²¹ (may remain unaltered for many years³⁰) epiphyseal necrosis possible⁴⁵

C LONG BONES

Some osteoporosis with sexual infantilism or marked hyperthyroidism, exostoses and overgrowth of tuberosities (compare with eunuch), increase in length of arms and legs when eunuchoid, radii greater than humeri, tibiae greater than femurs, necrosis of metatarsals may occur⁴⁵

D VERTEBRAE

Normal or wedging and osteoporosis, increased density (eburnization)⁴⁵

E BONE TEXTURE

Coarse trabeculations¹

F MISCELLANEOUS

1 Pelvis

May be feminine type²

2 Hip joints

Rarely osteochondritis deformans^{13 45}

3 Scaphoids (tarsal)

Occasionally Kohler's disease (fragmentation and increased density)⁴⁵

IX ETIOLOGY

A UNKNOWN

B HEREDITY—Possible tendency (see 9 XIV C and Protocol 9 \VIII)*^{19 41}

X PATHOLOGY

A GROSS^{3 8 23}

1 General splanchnomegaly which is often either

a Proportionate

b Disproportionate

2 Brain

a Normal⁴⁰b Enormous⁸

3 Pituitary tumor (see 2 IX A)

■ Size—large,^{20 22} but sometimes microscopic

b Surrounding tissues may be involved

4 Thyroid

■ Small

b Enlarged

■ Colloid goiter

5 Adrenals

a Small

b Large

6 Testes

a Involutd

b Hyperplastic

7 Pancreas

a Small

b Marked fibrosis

c Very large

8 Thymus

a Involutd

b Fatty tissue shreds

9 Spleen

■ Normal

b Enlarged

10 Bones (see 9 VIII) ^{1 2 33 34}

a Overdeveloped

b Well formed

c Very long

d Thick

e Heavy

f Muscular insertions prominent

g Ridges very rough

h Hyperostoses

i Exostoses (see Fig 69)

j Deformity of feet

k Genu valgum

l Arthritis

m Osteosarcoma

n Kyphosis

o Scoliosis

B MICROSCOPIC³³

1 Pituitary (duration and treatment may change histology) (see 2 IX B 12 b)

a Hyperplasia of acidophilic cells proportionate to degree of activity but picture is variable due to other factors too (see Protocol 9 \VI)¹¹

b Many multinucleated cells

c Chromophobe adenoma or mixed types have been noted

d Cystic degeneration may be found occasionally⁸

2 Testes

■ Semiferous tubules

(1) Normal^{12 19 20}(2) Mere ghosts of acini with absence of Sertoli cells⁵(3) Hyalinization³

(a) Variable amounts present

(b) Few tubules may be normal

- b Interstitial cells
 - (1) Number increased, but abnormal structure¹²
 - (2) Absent⁸
 - (3) Fibrotic replacement³
- Spermatogenesis—decreased³ *

XI PATHOLOGIC PHYSIOLOGY

A EARLY IN DISORDER

- 1 Essentially an overproduction of growth hormone occurring in a prepubescent individual
- 2 Other hormonal factors may be normal or deficient especially
 - Gonadotropins
 - b Adrenocorticotropin (probably)
- 3 Excess of growth hormone antagonizes adrenocorticotropin
- 4 Epiphyseal closure is thereby delayed thus permitting continued growth at an increased rate for an abnormal length of time
- 5 The changes are otherwise similar to acromegaly (see 10 I \), except for carbohydrate metabolism (see 2 VI B 3 d)

■ LATE IN DISORDER—Overactivity of growth promoting hormone may subside and marked hormonal deficiencies possibly result due to

- 1 Pressure from tumor
- 2 Treatment
- 3 Atrophic (exhaustion) changes

XII SYMPTOMATOLOGY

A FACTORS

- 1 Degree of hyperactivity of acidophilic cells
- 2 Intracranial pressure by expansion or extension of tumor
- 3 Duration of disorder
- 4 Complications
- 5 Associated diseases

B COMMON COMPLAINTS

- 1 Growth which has
 - a Increased markedly
 - b Continued beyond normal
- 2 Headache
 - a Location—variable
 - b Pain
 - (1) Mild
 - (2) Extreme
 - c Nausea and/or vomiting may occur
- 3 Visual disturbances

- 4 Fatigued easily⁶
- 5 Weakness
- 6 Irrascibility
- 7 Depression
- 8 Impotence
- 9 Amenorrhea
- 10 Difficulties due to skeletal abnormalities

XIII DIAGNOSIS

A SUMMARY

- 1 Growth rate
 - a Is abnormally increased
 - b Continues well beyond usual age of cessation
- 2 Sella turcica is enlarged in the majority of cases

B IMPORTANT DATA FOR CLINICAL STUDY

- 1 History
- 2 Physical examination
- 3 Previous measurements of height by checking school records to reveal time of
 - a Onset
 - b Rate of growth
- 4 Complete blood counts
- 5 Serum phosphorus (fasting)
- 6 Basal metabolic rate
- 7 Roentgenograms
 - a Skull
 - (1) Sella turcica—measurement of exact size
 - (2) Other changes
 - b Hand wrist for bone age
- 8 The following for future comparison
 - a Photographs
 - b Casts (face hands)
 - c Volume of water displacement by the extremities

XIV DIFFERENTIAL DIAGNOSIS

A ACROMEGALIC GIGANTISM^{1 14 19 22 27 31 33 37 43} (see Fig 64)

- 1 Onset during or after pubescence
- 2 Acromegalic features are prominent
- 3 Sella turcica
 - a Enlarged in majority
 - b Normal occasionally

■ EUNUCHOID GIGANTISM (hypogonadal gigantism)

- 1 Height—rarely over 7 feet
- 2 Span—greater than height
- 3 Acromegalic features—absent
- 4 Sexual organs—underdeveloped

- 5 17 ketosteroids—low
 - 6 Sella—not larger than normal, but may be in individuals who were castrated very early in life
- C UNUSUAL TALLNESS OR "ATAVISTIC" GIGANTISM** (see Figs 71 and 72) ^o
- 1 Normal, but extremely tall individual
 - 2 Family history of unusual height
 - 3 Development normal and proportionate
 - 4 Sexual findings—normal
 - 5 17 ketosteroids—normal
 - 6 Sella—not enlarged
 - 7 Bone
 - a Changes—absent
 - b Age—often advanced 1 to 2 years
- D MACROGENITOSOMIA PRAECOX**
- 1 Differentiation should be made in early childhood
 - 2 Precocious development of (see 92 V F)
 - a Skeletal growth but final height is less than normal
 - b Somatic features
 - c Genitalia
 - 3 17 ketosteroids—vary according to degree of precocity
 - 4 Sella—normal
- E HYPERTHYROIDISM**—Evaluation of findings during childhood, see 26 VI B
- XV COMPLICATIONS SEQUELAE AND ASSOCIATED DISEASES**
- A GENERAL**
- 1 Tumor changes
 - a Intracranial extension
 - b Spontaneous decompression followed by⁴
 - (1) Sudden recovery of sight
 - (2) Relief from somnolence
 - 2 Anemia
 - 3 Fatigability
 - 4 Impotence
 - 5 Sterility
 - 6 Social and economic difficulties
 - 7 Susceptibility to infection (see 99 II)
 - 8 Diabetes
- B BONES**
- 1 Orthopedic problems
 - 2 Arthritis (hypertrophic)³⁶
 - 3 Osteosarcoma
 - 4 Osteoma
 - 5 Osteitis deformans
- 6 Polyostotic fibrous dysplasia (see Protocol 9 XVI, Figs 67 and 74)
 - 7 Hyperostoses⁴
- C MISCELLANEOUS**
- 1 Hyperthyroidism (rare)
 - 2 Syringomyelia (unusual)
- XVI TREATMENT** (see Figs 61, 73, 76 and Chart 21)
- A OF PITUITARY TUMOR**
- 1 Roentgen¹⁵**
- a Indications
 - (1) Abnormal growth rate
 - (2) Evidence of tumor extension
 - (3) Visual
 - (a) Fields defective
 - (b) Acuity impaired
 - (4) Headaches
 - b Procedure—see 13 IX
 - c Subsequent management
 - (1) Second series advocated in 2 months if
 - (a) Growth rate is not satisfactorily retarded
 - (b) Phosphorus (serum, fasting) above 5 mg % for comparison the normal values are
 - [1] Before puberty, about 5 mg %
 - [2] After pubescence level declines to 3.5 mg % (average)
 - (2) Later irradiation is advisable if
 - (a) Abnormal growth rate resumes
 - (b) Secondary complications develop
 - d Results
 - (1) Abnormal growth retarded
 - (2) Other symptoms may be relieved
 - (3) Visual damages may be repaired
 - (4) Phosphorus (serum) declines
 - (5) Sella may decrease in size
- 2 Surgical¹⁶**
- a Indication—if roentgen therapy fails to control
 - (1) Growth
 - (2) Expansion of lesion
 - b Procedures—see 13 VII
 - c Results
 - (1) Growth acceleration—inhibited
 - (2) Intracranial pressure—relieved
 - (3) Phosphorus (serum)—decreases

d Postoperative irradiation (one series) is advisable about 2 weeks after surgery

3 Estrogens—see below

II HORMONAL

1 Indication—to promote sexual development if not present, thereby hastening

a Epiphyseal closure

b Growth cessation

2 Age for institution of therapy

a If pituitary gigantism is recognized and treated in childhood with roentgen therapy, hormones should be prescribed when normal adult height is

(1) Attained

(2) Probable within 5 years regardless of age²²

b Medication should be continued until bone age of at least 16 to 17 years has been reached

3 Preparations and dosages

a Gonadotropins (for males or females)

(1) Dosage—combined therapy parenteral²³

(a) Pituitary gonadotropins—150 to 300 ru daily

(b) Chorionic gonadotropin—500 to 2,000 ru daily

(2) Comment

(a) Patient may become resistant to these

(b) More practical to use than testosterone or estrogens

b Testosterone (for males)⁷

(1) Dosage

(a) Oral — methyltestosterone 50 to 100 mg daily

(b) Intramuscular — testosterone propionate, 100 mg or more weekly

(c) Pellets — testosterone 200 to 400 mg every 2 or 3 months as indicated by rate of absorption

(2) Comment

(a) Theoretically with the reduction of excess growth hormone by roentgen therapy testosterone should hasten epiphyseal closure

(b) Following intensive roentgen therapy or surgery tes

tosterone may be needed for its anabolic effects

c Estrogens (males and females)^{21, 24}

(1) Dosage

(a) Oral

[1] Stilbestrol—0.5 to 5 mg daily (gradually increase)

[2] Estrone (or conjugated estrogens)—0.6 to 6 mg daily

(b) Parenteral administration unnecessary

(2) Comment (see 10 XVI)

(a) Males

[1] Phosphorus (serum)

[a] Decrease suggests an inhibitory effect on growth (as in animals)

[b] Action on epiphyseal closure in gigantism is not known

[2] Objections (theoretical) may be overcome by simultaneous use of testosterone

[a] Breast enlargement possible

[b] Pituitary tumor size may increase

(b) Females

[1] Epiphyseal closure may be hastened (theoretical)

[a] Not by direct action but through the pituitary causing a release of adrenocorticotrophic hormone and gonadotropins

[b] With compression of cells by the pituitary tumor which make and store these factors it is doubtful that this action could take place until roentgen therapy has succeeded in relieving the pressure of the tumor

- [2] Pituitary may increase in size
- [3] Growth may be retarded more effectively⁹

C GENERAL

- 1 Anemia treated with iron or liver has little or no effect in these patients
- 2 Lassitude and/or somnolence—benzene sulfate (or similar preparations) dosage, oral—10 to 30 mg daily
- 3 Orthopedic problems
 - a Proper foot support
 - b Shoe fitting is important
 - Attention to
 - (1) Scoliosis
 - (2) Kyphosis
 - d Osteomas are removed if necessary
 - Epiphyses
 - (1) Irradiation should be considered in an 'all out' attempt to arrest growth
 - (2) Surgical treatment by exeresis
 - (a) Although not reported as having been done fixation of epiphyses might prevent unusual height if growth cannot be retarded otherwise
 - (b) Lower end of femurs and humeri would be sites of choice
 - 4 Observations in the future for
 - a General condition
 - b Growth rate
 - c Visual field changes
 - d Phosphorus (serum) level
 - e Sella size
 - (1) Decrease
 - (2) Increase

D HYPERTHYROIDISM

- 1 Iodine (Lugol's solution)
 - a Administration
 - (1) Alone (see 26 XVI B)

- (2) In combination with roentgen treatment
- (3) After thiouracil preparation for surgery (see 26 XVI E)
- b Dosage—oral, 10 minims tid pc in chocolate milk

2 Thiouracil derivatives (see 26 XVI D E)

- a Dosage—daily
 - (1) Thiouracil—0.4 to 0.6 Gm
 - (2) Propylthiouracil—0.3 to 0.4 Gm
- b Procedure—when basal metabolic rate is normal
 - (1) Reduce dose to one fourth of the original
 - (2) Start Lugol's solution preoperatively if surgery is planned
- 3 Roentgen therapy may be given over thyroid and/or pituitary to test its effectiveness (see 13 IV, 26 XVI G)
- 4 Subtotal thyroidectomy may be necessary after trial of above procedures

XVII PROGNOSIS (See Figs 61 65, 77)

A BENIGN TUMOR

- 1 Life expectancy is better than with malignant tumor nevertheless outcome is uncertain in either case
- 2 Average span is 21.3 years⁹
- 3 Few live to 50 years⁹

B THERAPEUTIC OUTLOOK

- 1 Logical and may be possible to arrest growth early but not enough patients have been treated
- 2 Recurrence of tumor after surgery has been observed
- 3 Sella may decrease in size
- 4 Secondary deficiencies may develop and require continued management

XVIII CAUSES OF DEATH

A INTERCURRENT INFECTION²⁰B INTRACRANIAL EXTENSION OF TUMOR³³

GIGANTISM PROTOCOL XV FIGS 61 62, 65, 66 69 73 75 76 CHARTS 18, 21

Family history Patient much taller than brothers and sisters.

Past medical Weighed 7¾ lbs at birth. Taller than average at 4 to 5 years. Did fairly well in school, but could not learn quickly

Chief complaint Rapid growth '6 inches in previous 6 months

Physical examination Age 15 male single. Weight 190 lbs Height 78¾ in (slightly stooped) Span 78½ in Pubic bone to floor 40 in BP 112/75 Shoe size 16 Hammer

toes, corns Skin pale Many freckles over face Head hair—long coarse dense, face, axillary and pubic hair are absent Facies normal Visual fields, acuity and optic disks normal Audiogram normal Penis and testes small Prostate not felt

Laboratory data RBC 3,400,000 to 4,400,000 Hgb 70% to 79% Blood sugar 69 mg % NPN 20 to 31 mg % Plasma cholesterol 92 to 170 mg % Glucose tolerance test normal Adrenal water test normal BMR minus 19% to minus 22% Urinary hormone studies FSH negative 17 ketosteroids 3.06 mg/24 hrs

Roentgenographic findings Skull on admission diameter 20 cm no change during observations Sella turcica 23 x 19 mm (790 sq mm), 6 years later 19 x 13 mm (387 sq mm) Frontal and maxillary sinuses grew larger Phalanges (terminal) tufting Heart not enlarged

MONTHS	BONE AGE	CHRONOLOGIC AGE
On admission	13	15
30	13	18
33	13.9	18
47	15.3	19
53	15.9	20
57	17.3	21

Treatment and progress Irradiation of pituitary during first 4½ years Patient grew 9 in in 6 years (see chart) No secondary sex characteristics after 2½ years of roentgen therapy Treated with chorionic and gonadotropic hormones from 2½ to 3½

years Dosage pituitary gonadotropin (300 ru per cc) 0.5 cc 6 times weekly, total 30,000 ru, and concurrently chorionic hormone of pregnancy urine (1,000 ru per cc) 1.5 cc 6 times weekly, total 300,000 ru Results of hormone therapy during first 3 months there was an increase in size of penis and testes with growth of pubic hair Erections and nocturnal emissions occurred By the tenth month, in spite of continued therapy there was a regression of all these changes Facial lanugo slight voice lower, and growth not stimulated Testosterone pellets 150 to 300 mg every 2 to 3 months, given for 5 to 5¾ years Testosterone in propylene glycol (oral) irregularly Secondary sex characteristics, return of pubic hair, frequent erections voice deeper, growth (longitudinal) arrested epiphyseal closure stimulated with testosterone No benefit with iron for secondary anemia Benzadrine 5 mg bid for lassitude Weight 230 lbs Final height 87¼ in Span 87½ in

Comment A typical pituitary giant, illustrating marked skeletal overgrowth with retarded bone age and without genital development beginning in early childhood The result of treatment was a slowing down of growth rate and epiphyseal closure concomitant with pituitary irradiation and administration of gonadotropic hormones and testosterone The case illustrates the presence of hypersecretion of growth hormone without evidence of excessive function of other pituitary hormones

GIGANTISM

Family history Other members tall

Past medical Age 7 to 8—increased height 74 in (tallest boy since first grade) Age 10 to 11—became deaf could not speak (an acute affair) Age 13—swelling of left side of face Age 15—diagnosed overactive pituitary but had no treatment In high school—eye changes first noted excellent student In college—good student Age 22—visual impairment severe

Chief complaint Trouble with his eyes

History of present illness Voice changed Beard absent Sexual development at high

PROTOCOL XVI FIGS 63, 67, 68, 74

school age Growth of 4 in in 2 years Hemianopsia

Physical examination Age 23, male, single Weight 278½ lbs Height 79¼ in BP 140/110 Gloves size 11 Fundi optic atrophy bilateral and bitemporal hemianopsia Visual acuity right 10/200 and left 20/100 Right eye pushed upward due to prominence of tight cheek Right sided facial paralysis Slight rubor in cheeks Teeth far apart Tongue normal Nasal twang Collar size 17 Thyroid 1½ times normal size Skin smooth warm, moist Female type of

pubic hair Swelling of breast bone and ribs over heart between nipple and manubrium, kyphoscoliosis present Penis 7 cm long Testes $2\frac{1}{2} \times 1\frac{1}{2}$ cm Right hip larger than left

Laboratory data Urine albumin 1 plus, sugar trace RBC 4,370 000 Hgb 10.9 Gm WBC 5,000 Differential polymorphonuclears 68%, lymphocytes 28%, monocytes 2%, eosinophils 2% Blood sugar 88 mg % Plasma cholesterol 152 mg % BMR plus 4% Two years postoperative (mail report) serum calcium 12.9 mg %, serum phosphorus 4.2 mg %, serum phosphatase 3.7 BU

Roentgenographic findings Skull—large cranial vault with overdevelopment of sinuses Large osteoma (osteoblastic overgrowth) arising from right parietal and occipital areas, extending over to involve the left occipital bone, right maxillary sinus and maxilla Another osteoma originates from the sphenoid to obliterate sphenoid sinus Sella, which is not enlarged, is pushed upward and carries the entire middle fossa with it, anterior clinoids are separated Moderate mandibular prognathism Bone age 17 years Pelvis—female type with some separation of pubis Valgus deformity of both hips A peculiar cystic bony overgrowth (polyostotic fibrous dysplasia) involving crest of right ilium

Treatment Operative note (abstract) by Dr

Gilbert Horrax Because of failing vision, an operation was undertaken as the best chance for recovering vision On account of the skull thickness the frontal sinus was deliberately opened with the usual bone flap The chiasmal region could not be exposed because of great tension, therefore, a tip of the right frontal lobe was quickly excised for adequate exposure A large dumbbell shaped tumor was extending from the sella under the frontal lobe, the upper end was about the size of a lime The tumor was sucked out, after opening and later removing the capsule Patient's condition was good during the procedure, which took 5 hrs Six postoperative roentgen treatments, 300 r each

Pathologic report Pituitary adenoma, chiefly chromophobe Bone—fibrosis and numerous osteoblasts and osteoclasts The pattern is unlike Paget's disease and more consistent with polyostotic fibrous dysplasia

Comment Gigantism with pituitary adenoma which was unrecognized until visual changes took place Sexual development slightly retarded Unusual bony overgrowth of skull and ilium with cystic areas in latter, possibly polyostotic fibrous dysplasia or simple hyperostosis Operative result for restoration of vision was excellent Patient incapacitated by bony deformities In view of his height, tumor may have had eosinophilic elements initially

PITUITARY GIGANTISM WITH NORMAL SEXUAL DEVELOPMENT

Family history Negative

Chief complaint Weakness

History of present illness At age of 11 years growth rate increased suddenly Height 160 cm at $10\frac{1}{2}$ years First seen by Dr Cushing in 1931 and reported by him (Dyspituitarism twenty years later, Arch Int Med 51:487-553 April 1933) A normally proportioned adolescent youth of 15, 6 ft $4\frac{3}{4}$ in tall (192 cm) and a span 7 cm greater than his height Weight 202 lbs Open epiphyses Roentgenograms of skull showed large accessory sinuses and a suspiciously large sella which measured 14×17 mm Possible bitemporal defects in visual fields BMR normal BP 110/70 Pituitary

PROTOCOL XVII FIG 64

irradiated on 2 occasions (1932), and during following 12 months there was only $\frac{5}{8}$ in growth in comparison with 3 in previously Patient grew until 19 years of age, then measuring 6 ft $11\frac{1}{2}$ in Entered Army in 1942 Two years later he noticed weakness of his legs, but otherwise he was in good health Normal sexual drive

Physical examination Age 31 male single Weight 295 lbs Height 84 in BP 130/90 No prognathism Facial, body, axillary and pubic hair normal Visual fields and acuity normal Thyroid normal Testes large Absent ankle jerks Slight hyposthesia Left knee jerk diminished

Laboratory data Urine negative Hgb 13

Gm Serum calcium 10.5 mg % Serum phosphorus 4.1 mg % Glucose tolerance normal BMR minus 9% 17 ketosteroids 20.5 mg /24 hrs

Roentgenographic findings Skull showed large sinuses and mastoids, sella 20 mm x 15 mm 280 sq mm Spine and chest negative

Comment Clearly a case of pituitary gigantism initially considered due to hyperplasia of eosinophilic cells and not a tumor Meas

urement of the lateral contour of the sella from the published skull roentgenogram (actual size) revealed an area of approximately 218 sq mm, indicating we believe an eosinophilic adenoma. It is assumed that local pressure effects of an expanding tumor were not sufficient to impair function of gonadotropic or other pituitary hormones. The muscular weakness of his legs was probably a peripheral neuritis occurring as the result of an acute upper respiratory infection.

ATAVISTIC GIGANTISM

Family history Grandfather was unusually tall. Parents normal.

Past medical At birth 9 lbs 5 oz, and 21 in. Participated in athletics. Mentally normal.

Chief complaint Growing too fast all his life.

History of present illness Patient grew about 2 to 2½ in a year. Between the ages of 12 to 13 he grew 4 in. and since then has averaged from 2 to 3 in a year.

Physical examination Age 15, male single. Weight 156½ lbs. Height 76 in. Span 79¾ in. BP 116/70. Body well proportioned. Hair normal. Genitalia normal. Other findings normal.

Laboratory data Urine complete blood count and glucose tolerance test normal. BMR minus 14%. Urinary FSH weak positive.

PROTOCOL XVIII FIGS 71, 72 CHART 20

17 ketosteroids 20.1 mg /24 hrs

Roentgenographic findings Skull normal. Bone age at 15 was 16 to 17 years. Terminal phalanges showed tufting.

Treatment None necessary.

Progress Final height 78¾ in. without shoes.

Comment This case illustrates an unusually tall individual who was normal in all other respects. His tallness might be considered atavistic in view of the great height of his grandfather in contrast with the normal stature of his parents. The possibility of a relative eosinophilic hyperplasia or adenoma cannot be excluded in these cases but failure of acromegalic changes after epiphyseal closure in most instances makes it unlikely.

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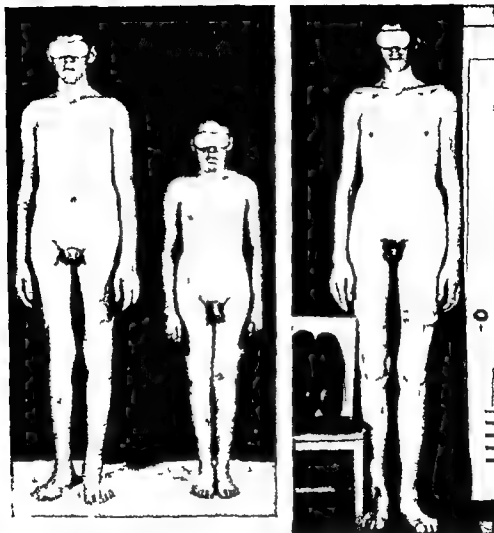


FIG 61 (Left) PITUITARY GIGANTISM (See Protocol 9 XV Figs 62 65 66 69 ,3 75 76 Charts 18 21) Patient age 15 beside boy of same age Before treatment Weight 190 lbs Height $78\frac{1}{4}$ in Span $78\frac{1}{2}$ in Pubis to floor 40 in

FIG 62 (Right) Six years later after roentgen chorionic and gonadotropic pituitary extract and testosterone therapy Weight 230 lbs Height $87\frac{1}{4}$ in Span $87\frac{1}{2}$ in



FIG 63 PITUITARY GIGANTISM (See Protocol 9 XVI Figs 67 69 74) Height $79\frac{1}{4}$ in Kyphosis decreases natural height Note marked distortion of face due to bony overgrowth (See roentgenograms of skull and pelvis) Subnormal development of genitalia with female escutcheon Sella turcica is not enlarged anterior clinoids are separated Dumbbell shaped pituitary tumor occupying sella and protruding up under right frontal lobe Bilateral hemianopsia Pathologic diagnosis pituitary adenoma chiefly chromophobes



FIG 64 PITUITARY GIANT WITH NORMAL GENITAL DEVELOPMENT (See Protocol 9 XVII)



FIG 65 PITUITARY GIANT AND DWARF
Pituitary giant (Protocol 9 \V) beside pi
tuitary dwarf (Protocol 3 IV) Prepuberal
hypopituitarism of approximately same
age 21



FIG 66 (Top) SKULL OF PITUITARY
GIANT (See Protocol 9 \V Figs 61 62 63
69 73 75 76 Charts 18 21) Brachy
cephalic type Prominent sinuses enlarged
sella no unusual prognathism

FIG 67 (Bottom) PITUITARY GIGANTISM
(See Protocol 9 \VI Figs 63 68 74)
Skull showing marked overgrowth of bone
(polyostotic fibrous dysplasia) Bone in
some parts 1 1/2 in thick Sella contour not
visible Large frontal sinuses Little if any
prognathism



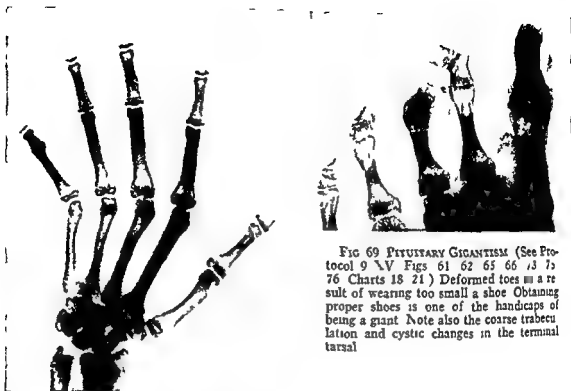


FIG 69 PITUITARY GIGANTISM (See Protocol 9 XV Figs 61 62 63 66 73 75 76 Charts 18 21) Deformed toes as a result of wearing too small a shoe. Obtaining proper shoes is one of the handicaps of being a giant. Note also the coarse trabeculation and cystic changes in the terminal tarsal

FIG 68 PITUITARY GIGANTISM (See Protocol 9 XVI Figs 63 67 74) Hand showing unusual position in which it was held by patient. Glove size 11



FIG 70 ACROMEGALIC GIGANTISM (See Chart 19) Sella upper limits of normal (right 126 mm left 61 mm) Oxygen encephalogram shown above reveals tumor extending through posterior capsule also some dilatation of anterior horn and body of left ventricle. Note also prominent sinuses and prognathism. Hemiplegia present on left

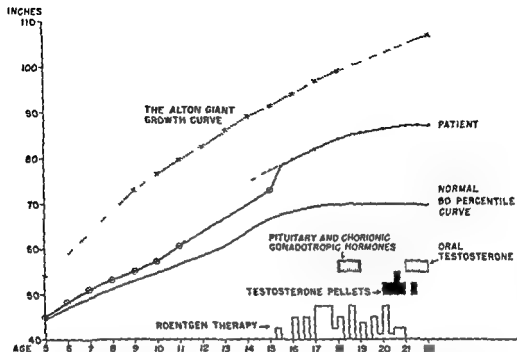


CHART 18 GROWTH CURVE OF PITUITARY GIANT AND THE ALTON GIANT (See Protocol 9 XV Figs 61 67 65 66 69 73 75 76 Chart 21) Circled dates represent heights obtained from school or home records. Solid dots represent observed heights at end of each year. If the last circled dot was an error then the dotted line can be assumed to be the rate of growth from 11 to 15½ years. If such is true there appears to have been little effect by irradiation therapy over the course of observation. Immediate effects of roentgenotherapy can be seen in Chart 21.

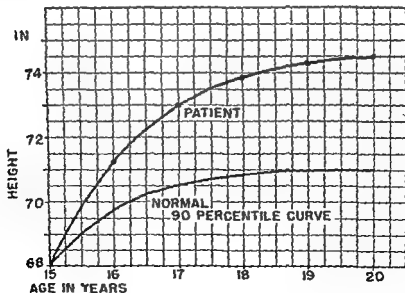


CHART 19 ACROMEGALIC GIGANTISM (See Fig 70) Growth curve of acromegalic giant compared with 90 percentile normal curve



FIG 71 UNUSUAL TALLNESS (See Protocol 9 XVIII Fig 72 Chart 20) Unusually tall boy of 15 Height 76 in Span 79 $\frac{3}{4}$ in Bone age 16 to 17 Predicted final height from bone age was 78 in Actual final height 78 $\frac{3}{4}$ in Although parents were not exceptionally tall (both under 72 in) the grandfather was regarded as a giant



FIG 72 SKULL OF UNUSUALLY TALL BOY (See Protocol 9 XVIII Fig 71 Chart 20) Except for normal size sella (52 sq mm) and normally shaped skull there is little difference between this skull and that of the pituitary giant pictured in Figure 66

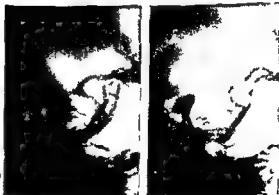


FIG 73 PITUITARY CIGANTISM (See Protocol 9 XV Figs 61 62 65 66 69 75 ,6 Charts 18 21) Sella turcica before (left) and after treatment Measurement before 23 x 19 mm (790 sq mm) After 5 $\frac{1}{2}$ years 19 x 13 mm (387 sq mm)

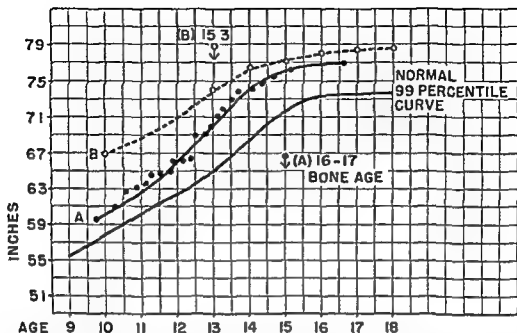


CHART 20 UNUSUAL TALLNESS (See Protocol 9 XVIII Figs 71 72) Growth curves of two unusually tall boys ('atastic gigantism') compared with the 99 normal percentile curve (Burgess) (A) Birth length 21 in Weight 9 lbs 5 oz Parents not tall Grandfather 76 in Bone age at 15 advanced (B) Birth weight 9 lbs 14 oz Parents and Siblings under 70 in Curve tapers off slower than curve A Bone age at 13 was 15 and growth continued for 4 years thereafter These curves illustrate variability of growth and the difficulty in estimating final height in a given case Puberty began at approximately the same time in both cases pubic hair present in both at 13 years of age



FIG 74 PITUITARY GIGANTISM (See Protocol 9 XVI Figs 63 67 68) A microscopic section of the spongy overgrowth of the skull which was removed during operation Note numerous osteoblasts and osteoclasts on surface of compact bone Fibrotic areas stain lightly (x 172)

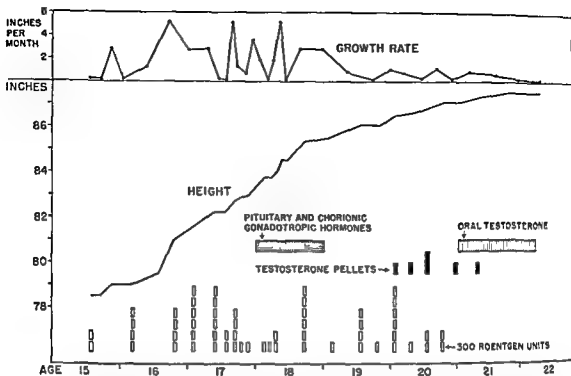


CHART 21 GROWTH AND TREATMENT CHART OF PITUITARY GIANT (See Protocol 9 XV Figs 61 62 65 66 69 73 75 76 Chart 18) Upper line represents the average growth rate per month (approximate) during the periods of time which followed roentgen treatment Before treatment began the average growth rate per month over a 4 6 year period was 0 31 in (99 percentile growth curve of Burgess between 11 and 15 years is 0 21 in per month) It is to be noted that this method of charting appears to depict growth changes dramatically although it is more sensitive to errors in recording height The effect of roentgen therapy is we believe, clearly shown

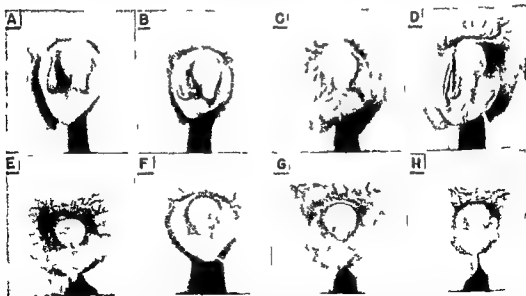


FIG 75 PITUITARY GIGANTISM (See Protocol 9 XV Figs 61 62 65 66 69 73 76 Charts 18 21) Genitalia before and after chorionic and pituitary gonadotropic therapy (330 000 units 11 months) regression after 1 year and return of pubic hair and other secondary sex characteristics after testosterone pellet implantation (A to E) At onset to end of gonadotropic and chorionic hormone therapy (F) One year after cessation of above therapy (G) After 16 months of testosterone therapy There was only a slight increase in size of testes (H) About 6 months after discontinuing testosterone

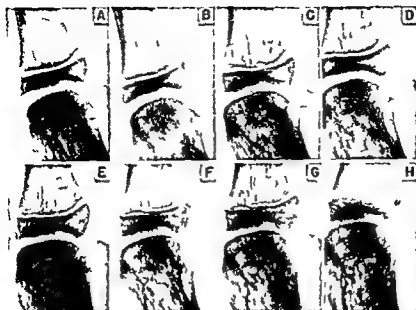


FIG 76 PITUITARY GIGANTISM (See Protocol 9 XV Figs 61 62 65 66 69 74 75 Charts 18 21) Epiphyses of first metacarpal phalangeal joint (A B C) During roentgen therapy of pituitary gland only for 28 month period (D E) During roentgen therapy plus chorionic and pituitary gonadotropic injections twenty eighth and thirty seventh months (F) Six months after cessation of treatment thirty seventh to forty third months (G) At beginning of testosterone therapy (H) Sixteen months after institution of testosterone therapy and cessation of longitudinal growth Note that epiphyses in A and D are essentially the same after $2\frac{1}{2}$ years of roentgen treatment alone and that closure appeared to begin after hormone therapy and was complete in 2 years



FIG 77 PITUITARY GIANT Typical pituitary giant with his father mother brothers and sisters Height 108 in Growth curve shown on Chart III

SECTION 10

ACROMEGALY

(Marie s Malady⁹⁰)

I DEFINITION	Acromegaly is a disease characterized by postpuberal hyperfunction of pituitary acidophilic cells causing progressive increase in the size of acral parts of the body
II APPEARANCE	Marked hypertrophy of all facial components, with big pawlike hands and feet, with or without spinal deformities height may be above normal, 'apelike' (see photos)
III AGE	Onset late in second decade or thereafter, 50 per cent begin in third decade ¹¹⁶
IV SEX	Males and females equally affected ¹¹⁶
V MENTAL DEVIATIONS	
A INTELLIGENCE	Variable
B RESPONSIVENESS	Often irritable, later irascible morose, apathetic, stuporous slow
C OTHER ABNORMALITIES	Memory usually not altered, introspective, may have psychoses
VI PHYSICAL STATUS	
A NUTRITION	Good
1 Weight	Normal or slightly increased unless complicated by severe hyperthyroidism
2 Fat distribution	Normal
B HEIGHT	Often normal depends on age of onset curvature of the spine decreases stature
C EXTREMITIES	
1 Upper	Proportionate to body size but seem small in comparison with hands joints are all big
a Hands	Pawlike enlarged in circumference but not lengthened grasp decreased (see Fig 79)
b Fingers	Normal length but appear short because of increased circumference ends bluntly rounded may show hypertrophic arthritis
■ Span	Not increased, unless dorsal round back or kyphosis ■ found
2 Lower	Proportionate to body size, joints enlarged, especially knees may be bowlegged
a Feet	Pawlike big (changes similar to hands), tendency to be flat plantar surface has deep folds and hypertrophied pads
b Toes	May be rounded thickened
D SPINE	Dorsal kyphosis lordosis and/or scoliosis may eventually develop

E. INTEGUMENT

1 General

a Texture

Marked hypertrophy of all subcutaneous tissues later atrophic changes deep folds at nasolabial area forehead scalp and shoulders also hands and feet have coarse heavy pads, flesh overhangs nails nail bed not widened Enlarged pores firm consistency but with subcutaneous softness

b Temperature

Increased in extremities may be from 2° to 3° above normal with or without hyperthyroidism due to increased vascularity of acral parts body temperature may be subnormal

c Moisture

Usually excessive often offensive in later stage, absent Acne warts, moles infection of apocrine glands mollus cum fibrosum, lipoma xanthomata

d Eruptions

Generalized or localized yellow or brown tinge occasionally vitiligo reported after estrogen therapy¹⁰⁸

e Pigmentation

f Color

Sallow, hands may be cyanosed at metacarpals because of extreme thickening of skin pallor late in disease¹⁹

2 Hair

a Head

Thick coarse rarely sparse and thin

b Facial

Males may have an increased amount females show excessive growth on chin and upper lip (see Fig 80)

c Axillary

May be increased

d Pubic

Normal or increased, scant rarely⁷³

e Body

Furry thick growth on limbs and trunk in some cases or may have hypotrichosis

F HEAD (see Figs 79 85)

1 Shape and size

Increased size, especially in circumference narrow and recessive forehead, prominent external protuberance of occiput malar bones conspicuous variable prognathism⁷⁰ face elongated and oval head may fall forward on chest Melancholic, emotionless passive stolid

2 Facial expression

3 Eyes

a General

Deeply seated rarely exophthalmos^{61 148} eyeballs reported enlarged eyelids thick eyelashes normal may have oculomotor palsy or palsies normal accommodation occasionally nystagmus increased lacrimation (if associated with hyperthyroidism see 26 VI A) conjunctivitis

b Fundi

May have optic atrophy or some optic edema (rare)

c Visual

(1) Fields

Variable defects may occur usually bitemporal hemia chromatopsia and/or central scotomata may precede optic atrophy (see Table 7 and Fig 91)⁶

(2) Acuity

Normal slight amblyopia or complete blindness

4 Ears and nose

Marked increase in length and width of nose with large nostrils alae thick mucous membranes and septum hypertrophied impaired sense of smell occasionally and/or deafness ears may be very large (see Fig 81)

5 Mouth and throat

a General

Marked hypertrophy and thickening of soft palate uvula and lips lower one may be everted tongue increased in size at times protrudes papillae are hypertrophied

b Teeth	Widely spaced, dental caries, loose, appear big, change of bite ¹⁻⁶
c Larynx (voice)	Hypertrophy of larynx and vocal cords, voice deep in both sexes unless secondary gonadal atrophy occurs prominence of thyroid cartilage
G NECK	
1 General	Short or long but always thick and heavy, sunken between rounded shoulders
2 Thyroid (see Fig 82)	May be palpable, hyperplastic or adenomatous ^{33 34 35 36}
3 Glands	Submaxillary and salivary are occasionally palpable
H CHEST	Normal or large in size with anteroposterior diameter greater in proportion to lateral, kyphosis and/or scoliosis and/or lordosis, "hunchback" appearance sternum may be protuberant, clavicles prominent, interspaces broadened and huge ribs
I HEART AND PERIPHERAL VESSELS	
1 Heart	Normal or may be enlarged ¹¹³
2 Rate and rhythm	Normal or tachycardia with or without hyperthyroidism, may have auricular fibrillation
3 Blood pressure	Variable elevated in 10 per cent ⁹⁰ less than 120 systolic in 30 per cent ^{70 116}
4 Peripheral arteries and veins	From normal to thickening and marked sclerosis of vessels veins are increased in size, varicosities common
5 Vasomotor	Flushed
J BREASTS	
1 Male	Lactation may be present, prominent, erectile nipples ^{13 3 123}
2 Female	Overgrowth or atrophy, may be lactating in absence of pregnancy ^{27 0 113 133}
K ABDOMEN	Pendulous
1 Liver	Occasionally enlarged, may be due in part to associated diabetes or congestive heart failure-- ^{55 116}
2 Spleen	Any size
3 Hernia	Not common
4 Tumor	None if kidneys sufficiently hypertrophied may be palpated
L GENITALIA	
1 Male	
a Penis	Enlarged proportionately
b Testes	Normal
c Prostate	Normal ⁷⁷
2 Female	
a External	Normal or enlarged
b Internal	Variable depending on stage of the disease often atrophic or infantile as expected with menopause
M NEUROMUSCULAR	
1 Muscles	Vary in development, depending on period of the disease, may be very muscular soft, flabby or atrophic
2 Gait	Normal or slow and cumbersome
3 Body movements	Normal or may be clumsy forward motion of spine limited

- 4 Tremor May be present with unilateral extension of tumor or hyperthyroidism
- 5 Paresthesias May occur
- 6 Reflexes Variable may show hemiplegia or paraplegia
- N SPEECH Normal or large tongue may interfere with distinct and free articulation

VII LABORATORY DATA

A URINE

- 1 General Normal volume variable
- 2 Special analyses
- a Sugar May be present without diabetes
 - b Albumin May be present
 - c Nitrogen Normal or decreased excretion (see below)
 - d Uric acid Increased output (endogenous)⁸¹
 - e Creatine Increased excretion but variable¹ = 1—125
 - f Creatinine As for creatine
 - g Calcium Increased output (dependent on activity of disease)¹ ^{14 16 47 81 103 109 11 17 140 147}
 - h Phosphorus Increased output^{16 40 48 81 16 100 11 1 140}
 - i Chloride Increased^{15 100}
 - j Iodine Normal or in excess if basal metabolic rate is elevated⁷⁷ =
 - k Magnesium Variable^{16 49}

B HEMATOLOGY

- 1 Red blood cells Normal or reduced in late stages^{23 4 76 151 11}
- 2 Hemoglobin Normal or low with progression of disease
- 3 White blood cells Normal or decreased in advanced cases
- 4 Differential Monocytosis slight increase in eosinophils and/or lymphocytosis

C BLOOD CHEMICAL ANALYSES

- 1 Sugar Variable often diabetic level (12%)^{77 83 6 93 133 141 151}
- 2 Nonprotein nitrogen Generally normal^{14 22 67} may be increased⁷⁶ = 1.0
- a Urea nitrogen As for nonprotein nitrogen^{76 1.0 131}
- 3 Protein Normal or upper normal^{152 101 1.4}
- a Albumin Normal
 - b Globulin Normal
 - c A/G ratio Normal
- 4 Uric acid May be increased occasionally^{73 76 80 1.0}
- 5 Cholesterol Variable may be very low even if basal metabolic rate is not elevated^{1 6 177 136}
- 6 Sodium Low normal¹³³
- 7 Potassium Low normal¹³³
- 8 Calcium Normal, may be decreased^{1 14 5 81 8. 1.1 126 127 130 156 147 1.0}
- 9 Phosphorus Normal or increased in active phase of disease^{71 81 83 119 130 135 138 147}
- 10 Phosphatase Normal^{1 81 129 135 147}
- 11 Chlorides Normal^{67 76 178}
- 12 Iodine Normal or increased^{53 116}
- 13 Creatine Increased²⁶
- 14 Creatinine Variable^{20 78 85}

D FUNCTION TESTS

1 Tolerance (see Chart 22)

a Glucose

Inconstant results, large percentage show decreased tolerance, rarely 'Houssay dog' phenomena (see 2 VI C 15, 10 V C 103 I D 1)^{3 14 17 22 23 30 35 67 75 78 83 85}
 91 9 98 100 106 1 1 6 13 135 137 138 147 149 151

b Glucose insulin

Inconstant results^{17 137}

■ Insulin

Variable results, hypoglycemic levels rarely^{33 136 137}

d Galactose

Normal or low in late stages¹

e Iodine

As in hyperthyroidism if present

f Creatine

Higher than normal, curve rises then tends to fall in 3 hrs^{6 177}

2 Adrenal water

No data, may be positive in "burnt out" cases⁷⁷

3 Salt deprivation

Normal or may be positive in advanced cases^{136 137}

4 Balance

a Nitrogen

Negative but this must be considered from point of view of active acromegaly and associated secondary endocrine activity, reported slightly positive^{1 13 16 3 40 48 67 88}
 81 10 100 11 1 4 13 140

b Calcium

Negative^{14 16 40 48 10 100 112 1 6 127 130 140} (question of thyroid or parathyroid influence^{1 81}), not related to basal metabolic rate, usually follows nitrogen balance, could be positive

c Phosphorus

May be negative or positive^{8 14 16 40 81 105 100 11 14}
 130 140

d Potassium

Normal^{68 105}

5 Renal

a Phenolsulfonphthalein

Normal^{67 76}

b Urea clearance

May be upper limit of normal¹¹

E MISCELLANEOUS TESTS

1 Basal metabolic rate

Elevated in 70 per cent of cases (not always associated with enlarged thyroid) (see 2 VI B 16)^{14 0 116 136 151}

2 Circulation time

Normal or increased if basal metabolic rate is elevated

3 Sedimentation rate

Normal

4 Specific dynamic action of protein

Normal³

5 Gastric analysis

Normal hypochlorhydria or achlorhydria^{51 85}

6 Electrocardiogram

Normal or degenerative changes^{1 6 151}

7 Spinal fluid

Normal¹⁵¹

8 Fecal excretion

■ Calcium

Normal¹⁴

b Phosphorus

Normal¹⁴

c Creatine

Normal^{123-1 7}

F URINARY HORMONE ASSAYS

1 Follicle stimulating hormone

Generally reduced (blood and urine) from pressure of tumor but depends theoretically on ability of basophilic cells to function if local pressure exists^{1 22 20 55 79 81}
 83 94 95 100 144 may be present at menopause in some cases roentgen therapy may decrease output

2 Luteinizing hormone

Active case may have increased amounts¹⁰⁰ stationary cases no increase (blood and urine)*

3 Estrogens

Variable but should follow activity of basophilic cells, as above⁶⁹

* Transplant of eosinophilic adenoma of acromegalic giant failed to produce any change in ovaries of mice
 220

4 Pregnanediol	If menses exist
5 17 ketosteroids	Usually normal or low but could be increased ^{1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100 101 102 103 104 105 106 107 108 109 110 111 112 113 114 115 116 117 118 119 120 121 122 123 124 125 126 127 128 129 130 131 132 133 134 135 136 137 138 139 140 141 142 143 144 145 146 147 148 149 150 151 152 153 154 155 156 157 158 159 160 161 162 163 164 165 166 167 168 169 170 171 172 173 174 175 176 177 178 179 180 181 182 183 184 185 186 187 188 189 190 191 192 193 194 195 196 197 198 199 200 201 202 203 204 205 206 207 208 209 210 211 212 213 214 215 216 217 218 219 220 221 222 223 224 225 226 227 228 229 230 231 232 233 234 235 236 237 238 239 240 241 242 243 244 245 246 247 248 249 250 251 252 253 254 255 256 257 258 259 260 261 262 263 264 265 266 267 268 269 270 271 272 273 274 275 276 277 278 279 280 281 282 283 284 285 286 287 288 289 290 291 292 293 294 295 296 297 298 299 300 301 302 303 304 305 306 307 308 309 310 311 312 313 314 315 316 317 318 319 320 321 322 323 324 325 326 327 328 329 330 331 332 333 334 335 336 337 338 339 340 341 342 343 344 345 346 347 348 349 350 351 352 353 354 355 356 357 358 359 360 361 362 363 364 365 366 367 368 369 370 371 372 373 374 375 376 377 378 379 380 381 382 383 384 385 386 387 388 389 390 391 392 393 394 395 396 397 398 399 400 401 402 403 404 405 406 407 408 409 410 411 412 413 414 415 416 417 418 419 420 421 422 423 424 425 426 427 428 429 430 431 432 433 434 435 436 437 438 439 440 441 442 443 444 445 446 447 448 449 450 451 452 453 454 455 456 457 458 459 460 461 462 463 464 465 466 467 468 469 470 471 472 473 474 475 476 477 478 479 480 481 482 483 484 485 486 487 488 489 490 491 492 493 494 495 496 497 498 499 500 501 502 503 504 505 506 507 508 509 510 511 512 513 514 515 516 517 518 519 520 521 522 523 524 525 526 527 528 529 530 531 532 533 534 535 536 537 538 539 540 541 542 543 544 545 546 547 548 549 550 551 552 553 554 555 556 557 558 559 560 561 562 563 564 565 566 567 568 569 570 571 572 573 574 575 576 577 578 579 580 581 582 583 584 585 586 587 588 589 590 591 592 593 594 595 596 597 598 599 600 601 602 603 604 605 606 607 608 609 610 611 612 613 614 615 616 617 618 619 620 621 622 623 624 625 626 627 628 629 630 631 632 633 634 635 636 637 638 639 640 641 642 643 644 645 646 647 648 649 650 651 652 653 654 655 656 657 658 659 660 661 662 663 664 665 666 667 668 669 670 671 672 673 674 675 676 677 678 679 680 681 682 683 684 685 686 687 688 689 690 691 692 693 694 695 696 697 698 699 700 701 702 703 704 705 706 707 708 709 710 711 712 713 714 715 716 717 718 719 720 721 722 723 724 725 726 727 728 729 730 731 732 733 734 735 736 737 738 739 740 741 742 743 744 745 746 747 748 749 750 751 752 753 754 755 756 757 758 759 760 761 762 763 764 765 766 767 768 769 770 771 772 773 774 775 776 777 778 779 780 781 782 783 784 785 786 787 788 789 790 791 792 793 794 795 796 797 798 799 800 801 802 803 804 805 806 807 808 809 810 811 812 813 814 815 816 817 818 819 820 821 822 823 824 825 826 827 828 829 830 831 832 833 834 835 836 837 838 839 840 841 842 843 844 845 846 847 848 849 850 851 852 853 854 855 856 857 858 859 860 861 862 863 864 865 866 867 868 869 870 871 872 873 874 875 876 877 878 879 880 881 882 883 884 885 886 887 888 889 890 891 892 893 894 895 896 897 898 899 900 901 902 903 904 905 906 907 908 909 910 911 912 913 914 915 916 917 918 919 920 921 922 923 924 925 926 927 928 929 930 931 932 933 934 935 936 937 938 939 940 941 942 943 944 945 946 947 948 949 950 951 952 953 954 955 956 957 958 959 960 961 962 963 964 965 966 967 968 969 970 971 972 973 974 975 976 977 978 979 980 981 982 983 984 985 986 987 988 989 990 991 992 993 994 995 996 997 998 999 1000}
6 11 oxysteroids	Normal or slightly increased ^{118 119}
7 Aschheim Zondek	Negative unless pregnant which is possible, ⁷⁰ occasionally positive in males and females ⁷³
8 Thyrotropic hormone	Increased (blood also) ^{46 111 131}
G BIOPSY	
1 Endometrial	Often atrophic but variable depending on ovarian activity
2 Testicular	See microscopic pathology
H VAGINAL SMEAR	Normal or atrophic
I SEMEN ANALYSIS	Normal or decreased count ^{1 83}
VIII ROENTGENOGRAPHIC FINDINGS (see Figs 86 to 90)	
A SKULL	
1 Cranial vault	Irregularly thickened prominent occipital protuberance malar and zygomatic bones hyperostoses, ^{70 151} osseous hypertrophy (see Protocol 9 XVI)
2 Sella turcica	Enlarged or eroded in over 90 per cent (although only 80% reported by Vaughn ¹¹⁵) may be unilateral, often extension into sphenoid sinus and nasopharynx (see 2 XIV G and Table 7)
3 Mandible	Slight to marked prognathism, may have subluxation
4 Sinuses	Usually enlarged and wide
5 Teeth	Widely spaced due to enlarged jaw and heaping up of alveolar arches ⁹⁰
B EPIPHYSEAL STATUS (bone age)	Closed epiphyses are broadened
C LONG BONES	
1 General	Occasionally increased in length at epiphyseal extremity, enlargement of head tuberosities muscular attachments spines and exostoses are common long bones widened may show hypertrophic arthritis periosteal ossification with pathologic proliferation of cartilage cystic degeneration ^{1 4 43 80 139 147}
2 Carpals	Increased in size and roughened surfaces
3 Tarsals	Enlarged less evident changes than with the carpals
4 Phalanges (terminal)	Often tufted however not diagnostic until late in disease
D VERTEBRAE	Hypertrophy and later ankylosis degenerative arthritic changes anteroposterior width increased 80 per cent of cases show spinal changes ^{7 4 43 147}
E BONE TEXTURE	Coarse spur formation advanced cases osteoporotic atrophy and rarefaction of cancellated bone vascular channels visible and large ⁸ cartilage may be calcified
F MISCELLANEOUS ¹³⁹	
1 Sternum	Hypertrophied protuberant
2 Scapulae	Normal or enlarged
3 Clavicles	Big thickened broad
4 Pelvis	Normal or enlarged
5 Patellae	Increased in all diameters
6 Kidneys	Normal size or enlarged stones may be noted ⁷¹
7 Stomach	More or less enlarged in most cases

IX ETIOLOGY

A UNKNOWN

B HEREDITARY OR CONGENITAL—Occurrence in members of same family has been reported^{10 53}X PATHOLOGY^{7 23 27 31 31 42 55 53 75 80 100 133 147}

A GROSS

1 Comment—generalized splanchnomegaly and adenomas of all organs, but at times within normal range

2 Pituitary (see 2 IX B 12 b)

a Normal^{10 38}

b Hyperplasia

■ Adenoma

(1) Acidophilic

(2) Outside of sella in path of Rathke's pouch (rarely)⁴¹

d Sarcoma¹¹⁷

e Cystic degeneration

f Cancer (unusual)¹³³

3 Thyroid⁴

a Normal

b Hypertrophy

(1) Unilateral

(2) General

c Atrophy

d Hyperplasia

e Adenoma

(1) Single

(2) Multiple

f Colloid degeneration

g Absent on one side

4 Parathyroids

a Hypertrophy

b Adenoma

(1) Single

(2) Multiple

5 Adrenals

a Normal⁴⁷

b Cortical adenomas—common

6 Testes

a Normal^{100 133}

b Hypertrophy¹³³

c Atrophy^{31 55 129 141}

7 Ovaries

a Atrophy^{5 47}

b Hypertrophic changes occasionally
^{53 141}

8 Pancreas

a Normal

b As in diabetes mellitus (in cases with glycosuria and hyperglycemia)⁷³

(1) Fibrosis

(2) Atrophy

(3) Hypertrophy

(4) Fatty degeneration

(5) Suppuration

(6) Interstitial hemorrhages

(7) Islet cells may be

(a) Atrophic

(b) Hyperplastic

(c) Absent

c Adenoma

d Enlarged

9 Thymus

a Present^{50 63}

b Absent⁶⁴

c Enormous^{9 8 6 116}

10 Liver

a Normal

b Hypertrophy (5 900 to 6,200 Gm)¹¹⁸

c Fatty degeneration

d Chronic congestion

e Hypertrophic cirrhosis

11 Heart

a Normal

b Hypertrophy (1,275 Gm)¹¹³

c Atrophy

d Endocarditis

e Valvular disease

f Coronary involvement

12 Kidneys

a Normal

b Enlarged

13 Spleen

■ Normal

b Enlarged

14 Prostate

a Normal

b Enlarged

15 Bones^{71 4 43 80 139 147}

a Heavy (see Fig 87)

b Thick increased in transverse diameter

c Long ones—wide

d Muscular attachments and ridges are prominent

e Surfaces roughened

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- j Cystic degeneration
- k Cartilaginous ossification

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 - (2) No special arrangement
 - b Tumor presses against remaining cells
 - c Few blood vessels present
 - d Adenoma may be encapsulated
 - e Mixed tumors nondescript
- 2 Testes
 - a Seminiferous tubules^{118 123}
 - (1) Hypertrophic
 - (2) Atrophic
 - (3) Fibrotic
 - b Interstitial cells^{116 123}
 - (1) Normal
 - (2) Hypertrophic
 - (3) Atrophic
 - c Spermatogenesis
 - (1) Normal^{1 80}
 - (2) Absent¹²³

- 3 Retention, for tissue synthesis, of
 - a Nitrogen
 - b Phosphorus

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- 1 FSH may be
 - a Decreased
 - b Increased
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 - a Excessive (probably) in early cases causing increased (?) libido in males
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- 1 It seems likely that some cases of acromegaly may be associated with an excess of other pituitary hormones besides the growth hormone
- 2 More recent studies on the pure growth hormone suggest that it has little effect on other endocrine glands⁹⁰

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IX ETIOLOGY

A UNKNOWN

II HEREDITARY OR CONGENITAL—Occurrence in members of same family has been reported^{10 89}X PATHOLOGY^{7 23 27 28, 31 4 5 53 7 80 120 133 147}

A GROSS

1 Comment—generalized splanchnomegaly and adenomas of all organs, but at times within normal range

2 Pituitary (see 2 IX II 12 b)

a Normal^{10 38}

b Hyperplasia

c Adenoma

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(2) Outside of sella in path of Rathke's pouch (rarely)⁴¹

d Sarcoma¹¹⁷

e Cystic degeneration

f Cancer (unusual)¹³³

3 Thyroid⁴

a Normal

b Hypertrophy

(1) Unilateral

(2) General

c Atrophy

d Hyperplasia

■ Adenoma

(1) Single

(2) Multiple

f Colloid degeneration

■ Absent on one side

4 Parathyroids

a Hypertrophy

b Adenoma

(1) Single

(2) Multiple

5 Adrenals

■ Normal⁴⁷

b Cortical adenomas—common

6 Testes

a Normal^{100 133}

b Hypertrophy¹³³

■ Atrophy^{31 5 129 141}

7 Ovaries

a Atrophy^{5 47}

b Hypertrophic changes occasionally^{33 141}

8 Pancreas

a Normal

b As in diabetes mellitus (in cases with glycosuria and hyperglycemia)⁷

(1) Fibrosis

(2) Atrophy

(3) Hypertrophy

(4) Fatty degeneration

(5) Suppuration

(6) Interstitial hemorrhages

(7) Islet cells may be

(a) Atrophic

(b) Hyperplastic

(c) Absent

■ Adenoma

d Enlarged

9 Thymus

a Present^{19 55}

b Absent⁶⁴

c Enormous^{20 53 62, 110}

10 Liver

■ Normal

b Hypertrophy (5,900 to 6,200 Gm)¹¹⁶

c Fatty degeneration

d Chronic congestion

■ Hypertrophic cirrhosis

11 Heart

■ Normal

b Hypertrophy (1,275 Gm)¹¹³

c Atrophy

d Endocarditis

e Valvular disease

f Coronary involvement

12 Kidneys

■ Normal

b Enlarged

13 Spleen

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b Enlarged

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H PARATHYROID STIMULATION (parathyroid hormone (?) and/or other causes)

- 1 Calcium metabolism stimulated
 - a Excretion increased
 - b Balance may be negative even with a positive nitrogen balance due to unknown factors
- 2 Nephrolithiasis is common

XII SYMPTOMATOLOGY^{19 7 8 70} 97 116

A EXPANSION OR EXTENSION OF TUMOR WITH INCREASED INTRACRANIAL PRESSURE

- 1 Neuromuscular complaints
 - a Headaches⁷⁰
 - (1) Location not consistent
 - (2) Most frequently
 - (a) Frontal
 - (b) Temporal
 - (c) Supraorbital
 - b Paresthesias
 - c Pains or burning in extremities
 - d Thermal sensitivity
 - e Weakness (may have sudden fatigue)
 - f Hemiplegia
 - g Paraplegia
 - h Somnolence
 - i Lethargy (often marked)
 - j Insomnia
 - k Failing memory
 - l Depression
- m Vertigo
- n Neuralgia—facial ache⁷¹ may occur⁹⁷
- o Lack of equilibrium
- p Convulsive seizures
 - (1) General
 - (2) Focal
- q Uncinate gyrus seizures are characterized by olfactory and gustatory auras without epileptiform convulsions⁷⁷
- 2 Special senses are affected
 - a Visual changes of variable degree
 - (1) Photophobia
 - (2) Conjunctivitis
 - (3) Strabismus
 - b Smell
 - (1) Impaired sometimes
 - (2) Epistaxis
 - (3) Periodic blood tinged and mucoid discharge

(4) Spinal fluid may leak with extension of tumor into sphenoid sinus

- c Taste may be involved
- d Ears
 - (1) Hearing impaired
 - (2) Tinnitus
 - (3) Intolerance to noise

B HORMONAL^{67 84}

- 1 Genito-urinary
 - a Impotence⁵
 - b Libido sexualis
 - (1) Lost
 - (2) Increased
 - c Menstrual periods
 - (1) Amenorrhea usually
 - (2) Irregular
 - (3) Prolonged
 - (4) Decreased
 - d Patient may become pregnant^{70 71}
110 136 149
- 2 Progressive aggregate increase in size of
 - a Facial components
 - b Hands
 - c Feet

C GENERAL

- 1 Gastro intestinal
 - a Polyphagia
 - b Polydipsia
 - c Bulimia
- 2 Cardiorespiratory
 - a Dyspnea
 - b Palpitation
- 3 Arthritis (hypertrophic)¹⁴⁷

XIII DIAGNOSIS

A ROUTINE PROCEDURES

- 1 History—see symptomatology
- 2 Physical examination—check especially
 - a Weight
 - b Height
 - c Hands and feet enlargement
 - d Dorsal round back or kyphosis¹³
 - e Perspiration
 - f Facial coarsening
 - g Prognathism
 - h Eyes
 - (1) Visual
 - (a) Fields
 - (b) Acuity
 - (2) Ocular fundi for
 - (a) Edema
 - (b) Atrophy

- i Tongue hypertrophy
 - j Thyroid size
 - k Pulse rate
 - l Blood pressure
 - m Tremor
 - 3 Laboratory data
 - a Urine for sugar
 - b Blood chemical analyses
 - (1) Sugar
 - (a) Fasting
 - (b) Two hrs after eating
 - (2) Phosphorus (serum fasting)
 - c Glucose tolerance test (2 hr)
 - d Basal metabolic rate
 - 4 Roentgenograms
 - a Skull (stereoscopic) for secondary changes
 - (1) Sinus development
 - (2) Prognathism
 - (3) Intracranial pressure evidence (undue motting)
 - (4) Sellar size including area of lateral contours
 - (5) Both clinoids is to
 - (a) Separation
 - (b) Decalcification
 - (c) Interclinoid distance (dorsum floor)
 - (d) Other abnormalities
 - b Air or oxygen encephalograms for extension of tumor (see 2 VIII F 5)
 - c Hands
 - (1) Bone age
 - (2) Recording of size
 - 5 Lumbar puncture for pressure readings
- II SUMMARY OF IMPORTANT CLINICAL DATA**
- 1 Irreducible minimum for diagnosis (active or inactive)
 - a Actual enlargement of acral parts must be established
 - b Hands and feet as well as facial alterations must have taken place simultaneously⁷¹
 - 2 Differentiation of active and inactive stages
 - a History to determine
 - (1) Onset
 - (2) Sweating
 - (3) Tachycardia
 - (4) Visual damage
 - (5) Menstrual change (unless at time of menopause)
 - (a) Amenorrhea
 - (b) Menorrhagia
 - b Laboratory data
 - (1) Phosphorus (serum, fasting) is increased, based on repeated determinations in absence of other causes of hyperphosphatemia
 - (2) Basal metabolic rate may be elevated
 - (3) Glucose tolerance curve is often the diabetic type which may persist after inactivation of acromegalic process
 - c Roentgenologic findings show progressive changes
 - d Most of the above may be equivocal in which case diagnosis of activity may have to be postponed until sufficient evidence is collected
 - (1) If patient is under 30 years of age activity is likely to be present
 - (2) Elevation of fasting serum phosphorus of 4.5 mg % or more is adequate to confirm excessive growth hormone activity⁷¹
- XIV DIFFERENTIAL DIAGNOSIS**
- 1 GIGANTISM—see 9 VIII
 - B ACROMEGALOID CONSTITUTION (congenital prognathism without acromegaly—see Fig 92)⁷⁰
 - 1 Absence of other acromegalic
 - a Signs
 - b Symptoms
 - 2 Sella turcica not enlarged
 - C HYPERTHYROIDISM AND DIABETES—Acromegaly should be considered in all cases (see 31)
 - D FUGITIVE ACROMEGALY (see Fig 93)⁷⁰
 - 1 Patients with enlarged sella and clinical hypopituitarism in whom there are traces of previously active acromegaly
 - Sinuses—prominent
 - b Hands and feet—large
 - c Acromegalic features—slight
 - 2 Mixed tumor probably containing chromophobe and chromophil cells, with the latter becoming inactive—see d(2) above
 - E AMENORRHEA
 - 1 Often first symptom of acromegaly

- 2 Other causes too numerous to list—see 61 II C, D
- F HYPERTROPHIC PULMONARY OSTEOARTHROPATHY**
- 1 Skull—normal
 - 2 Intrathoracic disease present
 - 3 Cervicodorsal kyphosis
 - 4 Hands and feet
 - a Shape—deformed
 - b Size—increased slightly
 - c Fingers
 - (1) Drumstick
 - (2) Curved nails
 - 5 It is not likely to be confused with acromegaly
- G ARTHRITIS (hypertrophic)**
- 1 Typical arthritic findings without involvement of skull
 - 2 No characteristic enlargement of
 - a Hands
 - b Feet
 - 3 Acromegaly always should be considered
- XV COMPLICATIONS SEQUELAE AND ASSOCIATED DISEASES**
- A TUMOR CHANGES**
- 1 Rupture of capsule is rare¹²³
 - a Pressure relieved
 - b Vision restored occasionally
 - 2 Hemorrhage is not infrequent with a sudden loss of vision⁷¹
 - 3 Extension
 - a Various neurologic effects
 - b Seepage of spinal fluid into nasopharynx from sphenoid sinus
 - 4 Recurrence
 - a Despite all forms of therapy
 - b Even when apparently inactive
- B HYPERTHYROIDISM (see 26 VIII)^{27 70 116}**
- 1 Incidence—30 to 70 per cent
 - 2 Onset—usually not early in disease
 - 3 Characteristics
 - a Similar to toxic adenomatous goiter
 - b Exophthalmos—less frequent
 - c Basal metabolic rate increased extrathyroidal factor may be responsible⁷
- C DIABETES MELLITUS (see 85 VII)^{14 23 49 71 117}**
- 1 Incidence
 - a Range—6 to 40 per cent^{6 18 22 71 78 93 116}
- b Hereditary tendency—21 per cent²²**
- 2 Onset (average)**
- a 9.5 years after acromegaly—
 - b Age—38.8
- 3 Characteristics⁷⁷**
- a Similar to ordinary diabetics in all features, except occasionally greater fluctuation in insulin requirement¹⁷
23 ■ 75 76 78 1 1
 - b More insulin resistant at times^{28 9 112 141} (estrogen may correct this¹)
 - c Spontaneous recovery in some^{3 16 38 7 70}
 - d Thyroidectomy may reduce insulin requirement⁸⁷
 - e Pituitary removal does not cure diabetes, but may be improved (see 2 VI C 15 Tables 101, p 1419 and 102, p 1426)⁸⁷
 - f Severity may indicate the degree of pituitary activity (?)^{10 118}
- D CARDIOVASCULAR**
- 1 Incidence
 - a Up to 75 per cent reported to develop heart failure²⁰
 - b One in 40 cases⁷¹
 - 2 Characteristics⁷⁰
 - a Size of heart is
 - (1) Not related to
 - (a) Intracranial pressure
 - (b) Hyperthyroidism
 - (c) Diabetes
 - (d) Hypertension
 - (2) Out of proportion to
 - (a) Muscular development
 - (b) Body physique
 - (3) Affected by minor factors as
 - (a) Chest deformity
 - (b) Displacement
 - b Associated findings in some cases
 - (1) Angina pectoris
 - (2) Hypertension
 - (3) Nephritis (vascular)
- E INTERCURRENT INFECTION**
- 1 Any kind may develop^{70 118}
 - 2 Bronchitis with emphysema
- F RARE FINDINGS**
- 1 Panhypopituitarism
 - 2 Pituitary myxedema¹⁵
 - 3 Hyperparathyroidism⁷⁰
 - 4 Addison's disease¹⁵
 - 5 Leukemia⁷¹
 - 6 von Recklinghausen's disease¹⁹

- 7 Syringomyelia^{18, 64}
- 8 Amyotrophic lateral sclerosis^{19, 10*, 20*}
- 9 Glioma
- 10 Tabes¹⁹
- 11 Parkinson's disease⁶⁴
- 12 Granulosa-cell tumor¹³⁴

XVI TREATMENT

A OBJECTIVES ARE RELIEF OF⁷¹

- 1 Tumor pressure and its effects from
 - a Expanding locally or extending to adjacent parts
 - (1) Headache
 - (2) Visual disturbance
 - (3) Mental or neurologic changes
 - (a) Convulsions
 - (b) Psychotic states
 - (c) Hemiplegia
 - b Expansion within the sella damaging the normal pituitary cells
 - (1) Impotence (males)
 - (2) Amenorrhea (females)
- 2 Hyperhormonal effects due to an over active tumor causing
 - a Enlargement of acral parts, diminution of tissue changes to normal may be possible in early cases
 - b Headache
 - c Hyperthyroidism
 - d Diabetes
 - e Cardiovascular symptoms
 - (1) Hypertension
 - (2) Congestive heart failure
 - f Bone alterations
 - (1) Arthritis—hypertrophic type
 - (2) Exostoses
 - (3) Kyphosis
 - (4) Orthopedic complications
- 3 Concomitant or late hypohormonal effects which may follow treatment or occur spontaneously
 - a Panhypopituitarism
 - b Selective pituitary hormonal deficiencies
 - (1) Gonadotropic
 - (2) Thyrotropic
 - (3) Adrenocorticotrophic

II ROENTGEN

- 1 Indications
 - a Active stage of disorder
 - b If the following visual changes providing they are not recent or sudden are found

- (1) Field defects
 - (2) Diminished acuity
- c Persistent
- (1) Amenorrhea
 - (2) Galactorrhea
 - (3) Headache

- 2 Procedure—over pituitary area (see 13 IX)^{14, 23, 29, 66, 71, 115, 149}
- 3 Results to be anticipated from first course of irradiation
 - a Improvement
 - (1) Favorable outcome
 - (a) Normal catamenia returns in younger females
 - (b) Tissue swelling regresses in part at
 - [1] Tongue
 - [2] Palms of hands
 - (c) Headache
 - [1] Is relieved temporarily
 - [2] Recurs even if disorder appears arrested
 - (d) Visual defects are
 - [1] Improved
 - [2] Eliminated
 - (e) Acute edema may
 - [1] Induce mental abnormalities
 - [2] Cause further visual alteration
 - (f) Serum phosphorus decreased
 - (g) Glucose tolerance may improve
 - (h) Basal metabolic rate lowered
 - (i) Sellar size decreases in majority
 - (j) Hyperthyroidism of clinical significance may be ameliorated
 - (k) Other changes take place gradually
 - (2) The above results indicate that the tumor is radiosensitive
 - (3) Regardless of beneficial effects another series probably should be given within 4 months after initial program
 - b No improvement
 - (1) Unless evidence of rapid extension of tumor (growth or hemorrhage) second series should be started

- (a) Two months after first series has been completed
- (b) Tumor may
 - [1] Not be radiosensitive
 - [2] Be cystic, filled with fluid and blood
- (2) After second course or if rapid expansion of tumor occurs in spite of irradiation, surgery is warranted for such symptoms as progression of
 - (a) Visual field defects (gross)
 - (b) Sellar size
 - (c) Acromegalic features
- c For continued hyperthyroidism or severe diabetes—see below
- 4 Subsequent management
 - a Periodic observation every 3 months
 - b Judge by
 - (1) Headache
 - (a) Severity
 - (b) Recurrence
 - (2) Visual fields and/or acuity changes
 - (3) Acral parts enlarging
 - (4) Serum phosphorus if persistent or return of high levels
 - (5) Basal metabolic rate increasing
 - (6) Sella turcica increasing in size
 - c Visual improvement may occur up to 18 months after roentgen therapy¹³
 - d Activity in some cases may subside and remain stationary indefinitely
 - e Irradiation may have to be supplemented by surgical removal of tumor in an estimated 15 to 30 per cent²¹
- C SURGICAL
 - 1 Indications
 - a Progression of disease in spite of roentgen therapy over period of 6 to 12 months
 - b Visual loss suggests hemorrhage within tumor or cyst, if
 - (1) Sudden
 - (2) Marked
 - c Neurologic complications
 - d Extension of tumor as shown by oxygen encephalograms
 - 2 Procedures—see 13 VII^{27 30 36 71 137}
 - 3 Results
 - a Surgical outcome closely follows those obtained by roentgen therapy except that it may produce improvement when the latter
 - (1) Has failed to be effective
 - (2) Can no longer be used
 - b Hypopituitarism is more likely to occur
 - Recurrence rate is reduced by post operative roentgen therapy
 - d Hyperthyroidism may not be relieved³⁷
- D HORMONAL^{1 36 67 71 81 8 170 138}
 - 1 Estrogens
 - a Indications
 - (1) Depression of excess growth hormone⁶⁷
 - (2) Amenorrhea—see below
 - (3) Menorrhagia—see below
 - (4) Persistent lactation—see below¹³⁸
 - b Dosage
 - (1) Oral
 - (a) Stilbestrol—0.5 to 5 m. daily (gradually increase)
 - (b) Estrone (or conjugated estrogens)—0.6 to 6 mg daily
 - (2) Parenteral administration unnecessary
 - c Results
 - (1) No change in¹¹⁰
 - (a) Urinary
 - [1] Creatine
 - [2] Creatinine
 - (b) Nitrogen balance
 - (c) Basal metabolic rate
 - (2) Decrease in^{71 110}
 - (a) Calcium (marked)
 - [1] Urinary
 - [2] Fecal
 - (b) Phosphorus
 - [1] Serum
 - [2] Urinary
 - (c) FSH
 - (d) 17 ketosteroids
 - (3) Increase in phosphatase (serum)
 - (4) General effects
 - (a) Weight increased
 - (b) Decrease (by water displacement) in
 - [1] Hands
 - [2] Feet
 - (c) Testicular biopsy (if normal before therapy) shows that¹¹⁰

[1] Leydig cells are

- [a] Absent
- [b] Decreased

[2] Tubules

- [a] Few remain
- [b] Spermatogenesis decreased

- [c] Basement membrane may be collagenous

d Objections (testosterone may overcome these effects³¹—see below)

- (1) Breast enlargement possible³¹
- (2) Testicular atrophy¹¹⁰
- (3) Pituitary tumor may increase in size (see Protocol 10 \VI\)¹¹

2 Testosterone^{41 16}

a Indications

- (1) Asthenia of severe degree
- (2) Panhypopituitarism which may occur subsequently in burnt out cases
- (3) Trial in patients with loss of libido
- (4) Menorrhagia—see below
- (5) Neutralization of undesirable effects from estrogen therapy

b Dosage

- (1) Oral or buccal—methyltestosterone 50 to 100 mg daily
- (2) Intramuscular—testosterone propionate 100 mg or more weekly
- (3) Pellets—testosterone 200 to 400 mg every 2 or 3 months as indicated by rate of absorption

E COMPLICATIONS

1 Hyperthyroidism (see 26 \VI)

a Mild—await result of

- (1) Roentgen therapy
- (2) Surgery (if required)

b Severe

- (1) Preparation with^{32 35-37 51 151}
 - (a) Iodine often ineffective
 - (b) Propylthiouracil^{1 1 71}
- (2) Dosage—oral
 - (a) Lugol's solution—10 to 30 minims daily
 - (b) Propylthiouracil—200 to 300 mg daily
- (3) Management (see Chart 24)
 - (a) Propylthiouracil (or another antithyroid drug) is given

until basal metabolic rate becomes normal

[1] Dosage may be reduced or maintained

[2] A longer time is required for response than ordinary hyperthyroid patient

[3] Lugol's solution (if not taken previously) for 10 days preoperatively

[4] Myxedema may be produced with possible enlargement of thyroid gland¹

(b) Subtotal thyroidectomy is performed if

- [1] Goiter is present
- [2] Patient is in good condition

(c) Roentgen therapy over pituitary continued as needed

(d) Basal metabolic rate may remain elevated without¹

- [1] Signs of hyperthyroidism
- [2] Palpable goiter
- [3] Effect from antithyroid drugs¹⁰⁸
- [4] Increased uptake of radioactive iodine¹⁰¹

2 Diabetes

a Management (see 85 \VI)⁷⁰

- (1) Customary regime as for all diabetic patients
- (2) Disease may be controlled to great extent by treatment of primary disorder as discussed with
 - (a) Roentgen therapy
 - (b) Surgery
 - (c) Estrogens^{1 1}

b Complications

- (1) As in other diabetics
- (2) Increase in insulin resistance suggests greater pituitary activity

3 Headache

a Temporary relief with

- (1) Roentgen radiation
- (2) Surgery
- (3) Analgesics
- (4) Sedatives

- b Doubtful value
 (1) Estrogens
 (2) Androgens
- 4 Menstrual disorders
 a Menorrhagia
 (1) Dosage
 (a) Oral
 [1] Stilbestrol—5 to 50 mg daily
 [2] Progesterone (buccal)—30 to 50 mg daily for 1 week, repeat in 21 days
 (b) Parenteral
 [1] Progesterone—10 to 20 mg daily for 1 week repeat in 21 days
 [2] Testosterone propionate—50 mg daily
 (2) Result—spontaneous recovery possible
 b Amenorrhea
 (1) Dosage
 (a) Oral
 [1] Stilbestrol—0.5 to 1.5 mg daily for 21 to 28 days
 [2] Progesterone (buccal)—30 to 50 mg daily during third week
 (b) Comment
 [1] Progesterone prescribed after stilbestrol if
 [a] Vaginal smear is estrogenic type
- [b] Bleeding does not follow
 [2] Estrogens in large and continued doses may increase size of tumor (see Protocol 10 VII, Fig 94, Chart 23)
 (c) Pituitary tumor may be temporarily more sensitive to roentgen therapy
 (d) Neither of these effects have been definitely proven
- 5 Persistent lactation
 a Dosage
 (1) Oral
 (a) Stilbestrol—1 to 5 mg daily
 (b) Methyltestosterone—20 to 50 mg daily
 (2) Parenteral—testosterone propionate, 25 mg daily
 b Comment—the above medications may be given if symptom is not arrested by roentgen or surgical therapy
- 6 Impotence—testosterone may be tried in the usual doses if there is no improvement with
 a Roentgen therapy
 b Surgery
- 7 Panhypopituitarism may develop with or without previous therapy for acromegaly
- 8 Lassitude and/or somnolence—benzedrine sulfate or similar preparations 10 to 30 mg orally daily

F RESULTS IN 20 CASES FOLLOWED FROM 3 TO 13 YEARS⁷¹

	NUMBER OF CASES
1 Roentgen therapy (initially)	16
a Satisfactory and with no progression of disorder	14
b Unsuccessful and followed by surgery	2
(1) First case—favorable for 3 months then died of meningitis	
(2) Second patient—progression arrested catamenia returned but headache persisted	
2 Surgery as initial procedure with removal of tumor tissue and followed by roentgen therapy	2
a Progression of disorder halted	
b Amenorrhea persisted in both (one a postmenopausal patient)	
3 Exploration of pituitary but tumor not removed (died later of leukemia)	1
4 Surgery for recurrence (improved after 2 operations but died following third recurrence inadequate roentgen therapy)	1

XVII PROGNOSIS

A GENERAL

- 1 It depends on
 - a Rapidity of development
 - b Nature of tumor
 - c Response to treatment
 - d Associated diseases
- 2 Spontaneous cessation of growth hormone activity is common

B DURATION OF VARIOUS TYPES^{60 71}

- 1 Benign—may be 50 years
- 2 Chronic—from 8 to 30 years
- 3 Malignant (acute)—from 3 to 4 years

XVIII CAUSES OF DEATH⁷¹

A FROM TUMOR

1 Extension

2 Hemorrhage

II CARDIAC COMPLICATIONS

- 1 Congestive heart failure
- 2 Auricular fibrillation
- 3 Coronary disease
- 4 Subacute bacterial endocarditis (rare)

C INTERCURRENT INFECTION (any kind)⁷¹

- 1 Pneumonia
- 2 Influenza
- 3 Bronchitis

D DIABETIC COMA

E NEPHRITIS

F LEUKEMIA

G OTHER DISEASES

ACROMEGALY

PROTOCOL XV

FIGS 88 91, 94

CHART 23

Family history Negative

Past medical Negative

Chief complaint Enlarged hands and feet

History of present illness Patient was rejected by the draft board because of acromegaly of which he was unaware. Shortly after puberty he started to grow rapidly until 19 years of age when he reached 78 in. Furuncles for 3 years under arms and on the buttocks. Shaves regularly. Sex function normal. No further increase in general size for 18 months. No headache or visual change.

Physical examination Age 21 male single. Weight 235 lb. Height 78 in. Span 79½ in. Pulse 96. BP 150/90. Increase in size of acral parts. Hair normal distribution. Thyroid and genitalia normal. Reflexes normal.

Laboratory data Urine normal. Glucose tolerance test (blood sugar mg %) fasting 100 ½ hr, 167 1 hr, 134 2 hrs, 78.

Roentgenographic findings Skull—sella enlarged, clinoids displaced backward, decalcification of anterior clinoids, enlargement mainly on left side. Epiphyseal status (bone age)—closed.

Progress

MONTHS

- 12 No complaints. Visual fields—slight defect in bitemporal fields. Visual acuity—little change.
- 20 Shoes the same. No tremor or sweating. Erections somewhat less. Weight 240 lbs. Height same. BP 130/80. Pulse 96.

Roentgenographic findings—see Table 7

- 32 Rarely headache. Loss of sight in right eye suddenly, 2 months previously. Roentgen therapy 1,800 r.
- 33 No ejaculations possible. Questionable hypoglycemic attack on one occasion.
- 35 Roentgen therapy 1,800 r.
- 37 Apocrine gland infection around perineum. Glucose tolerance test (blood sugar mg %) ½ hr 97, 1 hr 175, 2 hrs 189, 3 hrs 165. Roentgen therapy 1,800 r.
- 39 Serum protein 6.7 Gm %; Plasma cholesterol 54 mg %; Serum phosphorus 5.1, 4.7, 4.9 and 3.9 mg %* 17 ketosteroids 6.5 mg/24 hrs. Estrone 3 to 75 mg/24 hrs for 2 months. Stilbestrol 6 mg/24 hrs for another 7 months.
- 42 Sella turcica larger. Roentgen therapy 1,800 r.
- 51 Breasts enlarged and sore. Apocrine gland infection better. No headache. Shaves every day. Erections absent. Weight 248 lbs. BP 120/80. Hair decreased on body and chest. Breasts pigmented. Testicles smaller. Penis pigmented. Glucose insulin tolerance test no change. Roentgen therapy 1,800 r.
- 53 Head feels full. Very constipated.

* We are grateful to Dr. Ann P. Forbes for these reports.

Vision impaired Further therapy not recommended, operation advised

- 55 Hair on chest and around pubic area has fallen out Shaves less Breasts still show enlargement RBC 6,200,000 Hgb 13.1 Gm Differential count not remarkable Plasma cholesterol 66 mg % Serum phosphorus 5.5 mg % Adrenal water test normal Operation —right frontal craniotomy with removal of pituitary adenoma Serum phosphorus 7 mg % and 5.5 mg %, in first postoperative week.

- 58 Patient died at home 3 months later, from meningitis (postmortem examination)

Comment Hyperpituitarism beginning after onset of puberty resulting in partial gigantism and acromegaly Severe apocrine gland infection Patient responded to roentgen therapy for visual disturbance Estrogens caused atrophy of testes, breast development and may have increased the size of pituitary tumor Progressive enlargement of sella in spite of roentgen therapy necessitated an operation, which was performed successfully Death occurred 3 months later from an acute meningitis Pathologic diagnosis pituitary tumor compatible with the diagnosis of eosinophilic adenoma Eosinophilia was not demonstrated because specimen was unfortunately fixed in Zenker's solution with acetic acid

TABLE 7 ACROMEGALY

Measurements of sella over 4 year period by anteroposterior depth and lateral contour areas in square millimeters

MONTHS	RIGHT AREA IN SQ. MM.	LEFT AREA IN SQ. MM.	MEAN AREA IN SQ. MM.	RIGHT AP	RIGHT DEPTH	LEFT AP	LEFT DEPTH	ROENTGEN THERAPY IN R. UNITS	ESTROGEN (mg./24 hrs.)
On admission	290	486	388	23	15	23	22		
21	320	620	470	23	15	33	22		
34	258	793	520	24	15	35	27	1800	
36								1800	
38	258	793	520	25	22	35	30	1800	Estrone 3.75
40									
42	474	886	680	30	15	43	27		Estrone 3.75 Stilbestrol 6
45	325	590	407	26	20	38	25		Stilbestrol 6
49	598	810	707	33	21	37	25	1800	Stilbestrol 6
50									Stopped
52	506	939	722	30	20	42	27		
53	Operation								

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FIG 78 (Right) ACROMEGALY Probably the first published picture of acromegaly from Marie's original article (Marie P Sur deux cas d'acromégalie hypertrophie singulière non congénitale des extrémités supérieures inférieures et céphaliques Rev de méd 11 297 333)



FIG 79 (Below) PROGNATHISM IN ACROMEGALY Age 41 Duration 11 years Sella enlarged and depressed into spheroid sinus Slight temporal field defect Cervicodorsal kyphosis Amenorrhea menopausal Urinary FSH 3 plus Hand of patient compared with that of normal female on the right Note great overgrowth of tissue



FIG 80 LEONINA FACIES Age 29 male Showing deep furrows from overgrowth of facial tissues (leonina facies) Little or no prognathism



FIG 81 ACROMEGALY WITHOUT PROGNATHISM Age 32 Duration 2 years beginning after pregnancy Persistent lactation Headache No visual field defects Roentgen ray therapy (36 x 300 r) without effect on lactation or headache Temporary suppression of lactation with stilbestrol Increased size of sella Amenorrhea ceased after roentgen ray therapy



FIG 82 PROGNATHISM AND GOITER IN ACROMEGALY Age 34 Onset age from 14 to 15 gradual acral enlargement ceasing around age 30 Patient also had a nodular goiter and severe hyperthyroidism Complaints weight loss 50 lbs excessive perspiration palpitation weakness and severe back ache 3 years duration Bitemporal visual field defect enlarged sella depressed into sphenoid sinus Weight 145½ lbs Pulse 168 BMR plus 81% After 7 days on Lugol's solution weight 148 lbs Pulse 88 BMR plus 37% Subtotal thyroidectomy in 2 stages Weight 1 year later 189 lbs pulse 80 no hyperthyroidism Orthopedic examination flexion deformity left hip with no rotation Pronounced kyphosis low dorsal region Pain Degenerative changes shown on roentgenograms of spine and hip joint



FIG 83 ACROMEGALY WITHOUT PROGNATHISM Age 31 Onset from 7 to 8 years of age Amenorrhea since 19 Features gradually changed over a period from 1 to 8 years Gradual enlargement of hands and feet during 4 years Blurred vision and headaches for 1 year Loss of smell from 3 to 4 months Excessive sweating Musculature and body configuration has masculine tendencies Spadelike hands Note large nose and molluscum fibrosum Skin coarse Tongue normal Normal complete blood count fasting sugar total protein A/G ratio glucose tolerance test and glucose insulin tolerance test Sellar size 24 x 26 mm Roentgenography



FIG 84 ACROMEGALY IN A YOUNG FEMALE Age 20 Duration around 2 years Chief complaints swelling of hands and enlargement of face Marked acne Catamenia normal Blood pressure 160/110 Visual fields normal Serum phosphorus 5 mg % Plasma cholesterol 176 mg % Glucose tolerance curve ½ hr 96 mg % 2 hrs 204 mg % 3 hrs 163 mg % Note diabetic curve in disease of short duration Sella measured 15 x 18 mm area about 192 sq mm Progression in prognathism and sella size in spite of 16 x 300 r in 4 months of treatment Menorrhagia after first series of roentgen treatments Hypertension persisted and increased after therapy Rapid decrease in vision Operation and removal of adenoma followed by splanchuectomy BP normal 1 year later serum phosphorus 3.4 mg %

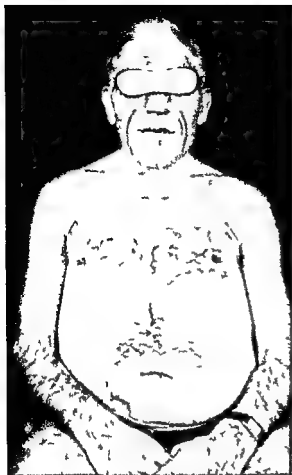


FIG 85 ACROMEGALY Age 56 Married at 22 Father of 3 children Acromegaly began at age of 40 although he noted no acromegalic changes until 50 years of age Patient never had body hair but after 40 it grew very rapidly He did not shave until 25 years old Patient has hypertension (BP 160/100) cardiac enlargement and coronary disease with transient nocturnal dyspnea and orthopnea EKG shows intraventricular block



FIG 86 ACROMEGALIC SKULL Age 36 male Duration 11 years Chief complaint supra orbital headache and transient blindness controlled by roentgenotherapy Leads normal life Father of 3 children since onset Note enlarged sella sinuses and prognathism

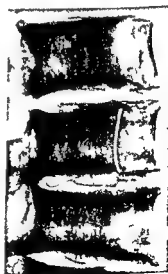


FIG 87 VERTEBRAE IN ACROMEGALY New growth (Erdheim J Die pathologische anatomischen Grundlagen der hypophysären Skelettveränderungen [Zwergwuchs Typus Frohlich Akromegalie Riesenwuchs] Fortschr a d Geb d Röntgenstrahlen 52 234)



FIG 88 PROGRESSIVE ENLARGEMENT OF SINUSES IN ACROMEGALY (See Protocol 10 \N Figs 91 94 Chart 23) (Left) First observation (Right) Observation 3 years later Note increase in size of frontal and maxillary sinuses

FIG 89 (Right) ACROMEGALIC GIANT SKELETON. Note especially arm length indicating span greater than height and onset before epiphyseal closure (Bassoe P Endocrine growth disturbance—acromegaly gigantism dwarfism \N Clin North Amer ica 5 85)



FIG 90 (Bottom) ACROMEGALY Age 51 female Duration from 10 to 12 years. Marked osteo-arthritic changes especially involving hip joints and preventing external rotation of legs



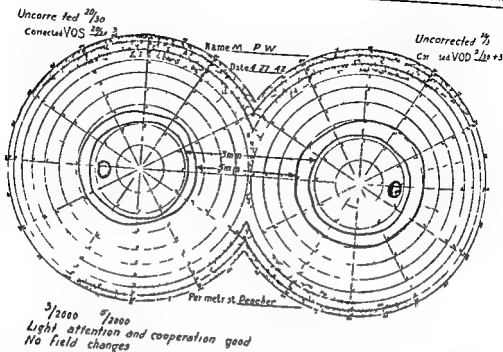
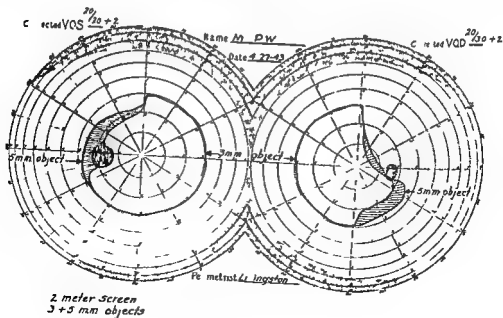


FIG 91 ACROMEGALY—VISUAL FIELDS (See Protocol 10 VII Figs 88 94 Chart 23) Visual fields in progressive acromegaly and immediate effect of roentgenotherapy. This case illustrates importance of early treatment and regular observation. (Above) On first examination (Below) One year later defects evident no visual disturbance noted by patient roentgenotherapy should have been given at this time (Opposite page top) Twenty two months later the patient first noted visual changes 2 months prior to this observation (Opposite page bottom) Six weeks after 6 roentgen ray treatments 300 r each further improvement did not take place in spite of 24 more treatments 300 r each during the ensuing year



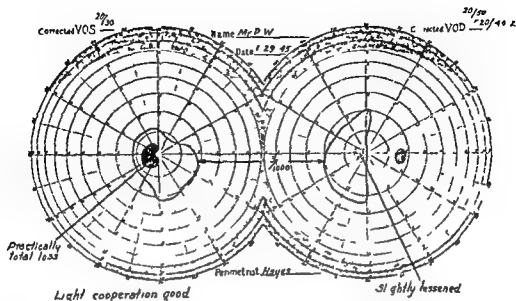


FIG 91 ACROMEGALY—VISUAL FIELDS Continued

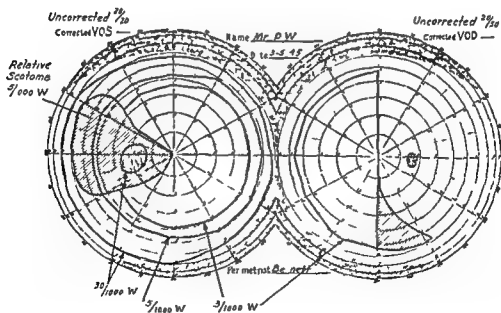




FIG 92 (*Left*) CONGENITAL PROGNATHISM
WITHOUT ACROMEGALY

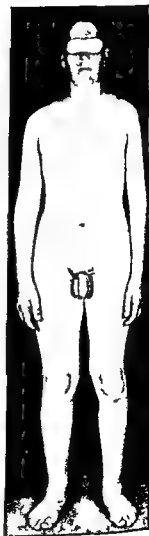


FIG 93 (*Right*) FUGITIVE ACROMEGALY Age 30 Although this patient had all the signs of a chromophobe tumor it should be noted that fairly large hands and feet prognathism and prominent frontal bossae are present Such findings would hardly be expected in view of a bone age of 16 if the entire process had been initiated by this type of tumor There fore it is probable that some hyperpituitarism existed for a few years and was followed by hypopituitarism His chief complaints were attacks of mental confusion depression agitation and loss of both libido and beard growth Repeated transient visual acuity changes were unrelieved by roentgenotherapy RBC 3.9 million Hgb 68% Plasma cholesterol 304 mg % BMR minus 32% Craniotomy by Dr J L Poppen Satisfactory response to oral testosterone therapy

CHART 22 ACROMEGALY Glucose tolerance curve in an acromegalic female (A) Before treatment weight 131 lbs pulse 72 BMR plus 4% (B) One year after treatment of pituitary tumor weight 151 lbs pulse 56 BMR minus 4%. Patient age 48 who had acromegaly probably 10 years or more was treated first with roentgenotherapy with temporary improvement in vision Later an operation was performed because of sudden and rapid visual failure Complete restoration of vision followed with no recurrence

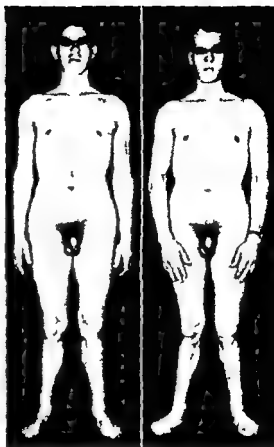
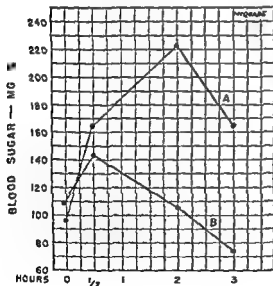


FIG 94 ACROMEGALY (See Protocol 10 VII, Figs 83-91 Chart 23) (Left) Age 20 Onset shortly after puberty Patient as he appeared on the first examination (Right) Patient immediately at the time of operation 4 years later Note loss of hair on abdomen and body as well as decreased amount surrounding pubic area There has been considerable atrophy of testes slight increase in size of breasts as well as darkening of the areolae This probably resulted from estrogen therapy There appears to be a change in stance Note also prominence of clavicles

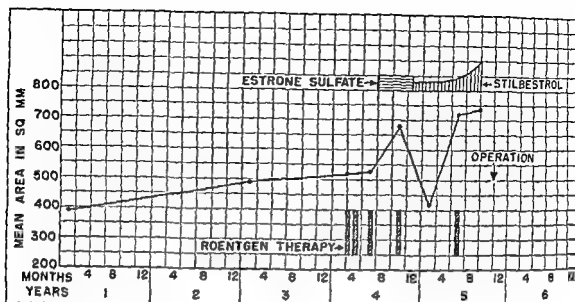


CHART 23 ACROMEGALY (See Protocol 10 \N Figs 88 91 94) Mean lateral contours of sella in square millimeters showing increasing size during observation during which time roentgen and estrogen therapy were given Possible deleterious effect of large doses of estrogens is suggested

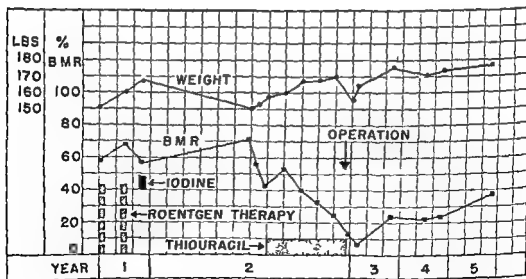


CHART 24 ACROMEGALY Chart of BMR and weight in acromegaly showing effect of thiouracil (0.6 Gm daily) Two courses of roentgenotherapy (2400 r each) had no effect Iodol's solution (30 mums a day) caused no clinical improvement Subtotal thyroidectomy was performed at end of second year Note gradual rise of BMR during 3 years after operation at which time the total blood iodine was 30.4 micrograms %

SECTION 11

CUSHING'S SYNDROME

(Pituitary Basophilism)

I DEFINITION

A condition which when fully developed is characterized by obesity of the trunk and the head, plethora, purplish striae of the skin hypertension and osteoporosis amenorrhea is almost always found in females impotence and atrophic testes may be present in males, slight to moderate hirsutism in females is often observed, polycythemia and glycosuria are frequently noted, the following outline pertains to Cushing's syndrome regardless of cause or age

II APPEARANCE

Buffalo type of obesity, moon face, hirsutism, plethora multiple pinkish to deep purple striae on protuberant abdomen upper arms and legs axillae and breasts when disease is fully developed (see Figs 95 98, 100 to 102)

III AGE

Any, third decade most frequent³⁴⁻³⁸

IV SEX

Females predominate

V MENTAL DEVIATIONS

A INTELLIGENCE

Normal variation or dull

B RESPONSIVENESS

Related to degree of mental aberration^{29 131}

C OTHER ABNORMALITIES

Usually depressed confused, anxious lethargic, may be psychotic late in disease, and have suicidal intentions (see Protocol 11 XXI)^{79 75 136}

VI PHYSICAL STATUS

A NUTRITION

Normal or obese thin extremities which may show muscular atrophy, undernutrition causes loss of weight as in normal person⁶⁰

1 Weight

Increased, may lose later in illness

2 Fat distribution

Rapidly acquired around face neck trunk abdomen may be painful face rarely involved alone⁶¹ unusual fat distribution may be due to skeletal deformity,⁶⁰ but this does not explain moon face (see 106 III E 13)

B HEIGHT

Normal or slight decrease if kyphosis or dorsal round back is present

C EXTREMITIES

Loss of flesh

1 Upper

Normal or appear thin and may show loss of weight

a Hands

Normal occasionally cyanotic

b Fingers

Normal occasionally cyanotic

■ Span

Normal relationship unless marked kyphosis

2 Lower

Thin in comparison with rest of body acrocyanosis of legs

■ Feet

Normal cyanosis and/or edema sometimes

b Toes

Normal occasionally cyanosis

D SPINE

Dorsal round back and/or kyphosis

E INTEGUMENT

1 General

Tight over obese areas nails brittle or hard

a Texture

Thin, little subcutaneous substance bruises easily parched texture¹

b	Temperature	Normal, but cold extremities with acrocyanosis at times
■	Moisture	Not remarkable
d	Eruptions	Acne, ecchymoses, telangiectasis ¹⁸
■	Pigmentation	May be some brownish discoloration small or large pinkish to deep purple (occasionally white) striae on abdomen, hips, axillae, arms, breasts (see Frontispiece) ³⁵
f	Color	Plethoric, cyanosis of hands, feet, face, mottling
2	Hair	
a	Head	Normal or brittle and dry, may show loss ¹¹⁴ ¹¹⁵ ¹⁵¹ hair line low on forehead ¹¹⁴
b	Facial	Slight to marked increase in females, no definite alteration in males perhaps less than normal ¹¹¹
■	Axillary	Normal, may be scanty ³⁷
d	Pubic	Normal, masculine distribution in females with adrenal tumor may be scanty ³⁷
e	Body	Occasionally marked hirsutism, less frequent in males
F	HEAD	
1	Shape and size	Normal but appears large and round
2	Facial expression	Moon face or pig eyed, dull, dreary
3	Eyes	
a	General	Appear small because of facial fat exophthalmos some times but slight (probably hypertensive feature) ⁹ ³ ⁵⁷ ⁹⁰ ¹¹⁴ ¹³⁵ ¹³⁷ ¹³⁸ ¹⁴ ¹⁸⁰ ^{19*}
b	Fundi	Normal optic edema if hypertensive with retinal hemorrhages and/or exudates ⁷⁸
c	Visual	
(1)	Fields	Normal could be reduced with pressure of large tumor ⁷⁸ ¹⁰⁸
(2)	Acuity	Normal unless reduced by hypertensive changes
4	Ears and nose	Normal
5	Mouth and throat	
a	General	Normal pig mouth
b	Teeth	Normal or carious periodontal membrane may be lost
■	Larynx (voice)	Variable
G	NECK	
1	General	Excessive fat short rounded and joins trunk with heavy fat pads
2	Thyroid	Normal rarely palpable
H	CHST	Normal contour except for dorsal round back and/or kyphosis
I	HEART AND PERIPHERAL VESSELS	
1	Heart	Normal or enlarged from hypertension
2	Rate and rhythm	Normal unless cardiac decompensation
3	Blood pressure	Rarely normal usually elevated with relatively high diastolic pressure
4	Peripheral arteries and veins	Normal or forceful pulsations with hypertension
5	Vasomotor	See Integument E1
J	BREASTS	
1	Male	Normal
2	Female	Normal may show striae or galactorrhea ¹¹⁷ if onset starts before puberty no development ¹³⁰

K. ABDOMEN	Protuberant
1 Liver	Normal
2 Spleen	Normal
3 Hernia	None
4 Tumor	Adrenal or ovarian (see Differential Diagnosis)
L. GENITALIA	
1 Male	
a Penis	Normal or atrophied in adults retarded and small if onset occurs before puberty (see Protocol 11 \\\)
b Testes	Normal size and consistency or some atrophy
■ Prostate	Normal ²⁸
2 Female	
a External	Normal or slight enlargement of the clitoris which is most marked with an adrenal tumor ²³
b Internal	Normal may have enlarged cystic or atresic ovaries ³⁸
M. NEUROMUSCULAR	
1 Muscles	Often severe weakness
2 Gait	Normal, unless vertebrae affected by multiple fractures and collapse, or when associated with weakness standing or walking may be impossible
3 Body movements	Normal
4 Tremor	May occur ^{114 115}
5 Paresthesias	May be present
6 Reflexes	Normal
N. SPEECH	Normal

VII LABORATORY DATA

A. URINE	
1 General	Normal volume may be increased
2 Special analyses	
a Sugar	May be present often excessive
b Albumin	Occasionally present
c Nitrogen	Variable
d Creatine	Normal ¹² or increased ¹¹
e Creatinine	Low excretion, may be half of normal ^{1 3 11 93}
f Sodium	Decreased ^{8 199}
g Potassium	Increased ⁸
h Calcium	Normal or slight increase
i Phosphorus	Variable ^{15 162 167}
j Iodine	No data
B. HEMATOLOGY	
1 Red blood cells	Normal or polycythemia ^{11 38 78}
2 Hemoglobin	Normal or increased ^{75 78}
3 White blood cells	Normal or increased (about 10 000 to 12 000) ¹⁰
4 Differential	Normal absolute or relative polymorphonuclear leukocytosis marked and absolute lymphocytic leukopenia ¹⁰ total eosinophils below 150 cu mm ¹⁶⁷
5 Hematocrit	Increased ⁵
6 Platelet count	Normal ^{117 118}
7 Fragility	Normal ¹⁸⁸
8 Bleeding time	Normal ⁷⁸
9 Coagulation time	Normal ⁷⁸
10 Clot retraction	Normal ⁷⁸

11 Reticulocytes	Normal ¹¹⁷
12 Prothrombin time	Normal or slightly prolonged ³⁹
C BLOOD CHEMICAL ANALYSES	
1 Sugar	Normal or high (for references see D a below)
2 Nonprotein nitrogen	Normal or increased ^{27 31 38 4 (3 7 III 114 174 201}
a Urea nitrogen	As for nonprotein nitrogen ^{18 80 90 100 13 137 138 144 151 164 187 188 190}
3 Protein	Normal or slightly decreased ^{6 7 37 2 4 3 80 88 92 125 100 164 1 3 174 188}
a A/G ratio	Normal or increased ^{37 43 48 90 188}
4 Uric acid	Normal ^{31 37 60 137}
5 Cholesterol	Variable ^{18 37 39 41 45 43 44 III 4 III 80 90 98 100 111 117 121 177 137 140 144 143 164 174 185 193 201}
6 Sodium	Normal, increased or decreased rarely ^{3 4 8 43 88 65 114 11 1 1 7 193 173 190}
7 Potassium	Normal or decreased ^{4 8 60 114 144 1 7 188 190}
8 Calcium	Usually normal, may be decreased ^{17 18 30 31 37 39 43 45 58 69 77 80 90 98 114 117 177 132 111 143 147 164 174 184 187 188 193 199 91}
9 Phosphorus	Normal or decreased (see Protocols 11 XXII XXIV) ^{11 33 53 9 77 78 80 94 98 99 10 117 1 7 140 148 167 184 174 185 187 188 191 190 90 91}
10 Chlorides	Normal or decreased ^{37 39 43 45 53 III 10 114 177 184 187 188 190}
11 Phosphatase	Normal or increased (see Therapy) ^{39 43 45 53 80 90 92 114 117 140 143 164 187 193 200}
12 Iodine	No data
13 Creatine	Increased ¹⁹³
14 Creatinine	Normal ^{31 37 193}
15 Magnesium	Variable ^{90 1 7 183 190}
16 Carbon dioxide combining power	Normal or increased ^{17 45 90 137 155 188 190}
17 Icterus index	May be increased
D FUNCTION TESTS	
1 Tolerance (see Chart 25)	
a Glucose	Normal, but more often diabetic curve ^{1 3 4 8 18 5 80 81 33 37-39 43 45 49 53 56-5 61 63 3 77 80 90 98 10 108 113 114 116 117 121 13 137 14 143 164 174 18 185 187 190 193 90 91}
b Glucose insulin	Decreased (hyperglycemic unresponsiveness) ^{3 6 7 174}
c Insulin	Curve shows resistance ^{1 39 56 7 174}
d Galactose	Normal, low or rarely high curve ^{1 8}
2 Adrenal water	Positive or negative ¹¹³
3 Salt deprivation	Decreased capacity for excreting chlorides in high concentration ^{6 4 143 164 188} (DOCA does not cause sodium chloride retention, as in normals, ^{24 143} when the latter is given intravenously—see 2 XIII E 2 b)
4 Balance	
a Nitrogen	Negative early in disease later may be slightly positive ^{1 4 37 38 43 99 140 147 156 190}
b Calcium	May be negative usually follows nitrogen balance ^{1 15 11 77 98 104 137 140 143 183}
c Phosphorus	Normal ^{15 38 88 102}
d Iodine	No data

5 Renal	
a Phenolsulfonphthalein	Normal or decreased
b Clearance	
(1) Urea	Normal or decreased ^{7,8}
(2) Creatinine	Normal ¹¹⁴
E MISCELLANEOUS	
1 Basal metabolic rate	Rarely above plus 20 per cent or below minus 20 per cent
2 Circulation time	Normal unless cardiac failure
3 Sedimentation rate	Variable, theoretically should be low ^{39 83 87 114 115 158}
4 Specific dynamic action of protein	Increased ^{137 161}
5 Gastric analysis	Normal or achlorhydria ^{48 99}
6 Electrocardiogram	Normal or myocardial damage ^{3 39 54 67 77 98 116 153}
7 Blood volume	Not increased ¹
8 pH	Increased ¹⁰⁶
9 Total base	Decreased ^{10 77}
10 Spinal fluid	Iressor substance negative ^{1 7 153 160}
11 Fecal excretion	
a Calcium	High ^{14 59}
b Phosphorus	High ⁹
F URINARY HORMONE ASSAYS	
1 Follicle stimulating hormone	Variable, usually less than normal ^{7 31 3 34 50 51 61 63 66 80 87 88 113 137 143 16 191 201}
2 Luteinizing hormone	No data
3 Estrogens	Variable, generally lower than normal ^{7 8, 4 64 6, 101 113 115 137 153 16 191 19}
4 Pregnanediol	May be present with amenorrhea ¹⁴⁵
5 17 ketosteroids	Normal or slightly elevated rarely markedly elevated ^{1 3 4 7 23 2 30 3 43 43 48 51 57 66 68 114 120 140 145 148 153 161 163 177 186 191 193 19}
6 11 oxysteroids (glycogenic units)	Upper normal to greatly increased (also in blood) ^{1 6-8 22 41 4 143 173 17 186 197}
7 Aschheim Zondek	Negative ^{17 19 45 50 68 75 81 90 107 113 1 4 16} or positive ^{34 57 154}
8 Thyrotropic hormone	Negative or increased ^{7 33 160}
9 Corticotropin	Increased (also blood) ^{14 76 8 8 143}
G BIOPSY	
1 Endometrial	Hypoplastic ¹¹⁴
2 Testicular	See 11 A B 2
H VAGINAL SMEAR	Low to moderate estrin effect even with amenorrhea ⁷⁸ neoplasticlike cells reported with normal catamenia ⁴
I SEMEN ANALYSIS	Normal or decreased count

VIII ROENTGENOGRAPHIC FINDINGS

A SKULL	
1 Cranial vault	Normal later shows progressive decalcification (osteoporosis) may have mottling or ground glass appearance
2 Sella turcica	Normal rarely enlarged (see Protocol 11 XXIV) ^{78 108 114}
3 Mandible	Normal
4 Sinuses	Normal
5 Teeth	Normal

- B EPIPHYSEAL STATUS**
(bone age) Normal rarely delay in prepubescent union of epiphyses
37 45 58 179 1.0 187 201
- C LONG BONES** Normal, except for decalcification and if marked may result in fractures, fragmentation of heads of femurs and metatarsals
- D VERTEBRAE** Kyphosis, may have collapsed multiple fractures, ankylosis, fish spine, decalcification with thin biconcave bodies separated by large intravertebral disks (expanded nucleus pulposus^{3 58}), special predilection for vertebrae and pelvis⁷
- E BONE TEXTURE**
- 1 Osteoporosis Cranium, pelvis, spine
 - 2 Fractures Spontaneous (see Fig 99)
- F MISCELLANEOUS**
- 1 Chest Lower ribs are enlarged and some may be fractured¹⁷⁹ callous formation seems adequate sternum may be protruberant from collapsed ribs, thymoma may be found^{179 187}
 - 2 Pelvis May show decalcification

IX ETIOLOGY

- A UNKNOWN**—Question of excessive secretion by basophilic cells due to
- 1 Overstimulation (possibly through hypothalamus⁷²—see 88 VIII k.)
 - 2 Abnormal cell rests
- B PITUITARY**—Basophilic adenoma may or may not be found
- C ADRENAL CORTEX**⁷¹
- 1 Hyperfunction
 - 2 Hyperplasia
 - 3 Carcinoma
 - 4 Adenoma (see Protocol 11 VIII Fig 98)
- D OTHER CAUSES** (see Pathology)
- 1 Carcinoma
 - a Pituitary
 - b Thyroid (see Frontispiece)
 - 2 Granulosa cell tumor
 - 3 Arrhenoblastoma (?)
 - 4 Thymic tumor
 - 5 Hypothalamic nuclei atrophy
 - 6 No gross pathology^{41 45} ■
- X PATHOLOGY**
- A GROSS**^{19 37 39 50 58 61 98 107 13 133 151 173 187 189}
- 1 Pituitary¹⁷⁸
 - Normal^{41 45 68}
 - b Adenoma
 - (1) Chromophobe^{37 61}
 - (2) Acidophilic⁷⁶
 - (3) Basophilic³⁰ ■
 - (4) In pars intermedia^{119 119}
 - c Sarcoma¹⁹⁴
 - d Carcinoma (may metastasize)^{5 54}
 - 2 Thyroid
 - a Normal
 - b Small
 - c Enlarged
 - d Adenoma
 - Colloid goiter with adenoma
 - f Atrophy
 - 3 Parathyroids
 - a Normal
 - b Atrophy³⁷
 - c Enlarged
 - d Adenoma^{37 58}
 - 4 Adrenals
 - a Normal
 - b Cortical hyperplasia
 - c Adenoma
 - d Carcinoma
 - e Fatty degeneration
 - f Tumor with atrophy of peripheral normal gland tissue
 - 5 Testicles
 - a Normal
 - b Small
 - c Atrophy
 - 6 Ovaries
 - a Normal
 - b Senile with cysts

- c Fibrosis
- d Atrophy
- e Enlarged and contain corpora lutea
- f Granulosa-cell tumor
- g Sclerotic
- h 'Adrenal like' tumor⁹³
- i Arrhenoblastoma (?)¹³¹
- 7 Pancreas
 - a Normal
 - b Atrophy with arteriosclerosis of islets of Langerhans
 - c Enlarged
 - d Fatty degeneration
- 8 Pineal
 - a Normal
 - b Enlarged
- 9 Thymus
 - a Involved usually^{35, 36}
 - b Carcinoma^{69, 106}
 - c Enlarged^{48, 170}
 - d Replaced by fat^{128, 180}
- 10 Kidneys
 - a Normal
 - b Malignant nephrosclerosis
 - c Nephritis¹⁷⁰
 - d Stones
- 11 Liver
 - a Normal
 - b Nutmeg³⁰
 - c Focal fatty degeneration⁷³
- 12 Spleen
 - a Normal¹⁸⁰
 - b Atrophy⁶¹
 - c Hyperplasia⁷³
- 13 Lymph nodes are atrophic
- 14 Bones
 - a Normal
 - b Osteoporosis
 - (1) Very soft¹⁵¹
 - (2) Crack easily
 - c Fibrous osteitis
 - d Osteomalacia (?)⁷³
 - e Hyperostosis⁵
- 15 Atherosclerosis (generalized)³⁸

II Microscopic

- 1 Pituitary
 - a Various types of adenomas have been found
 - b Basophilic adenoma is the most common¹⁷⁸
 - (1) Size
 - (a) Macroscopic
 - (b) Microscopic

- (2) It may be present in
 - (a) Normal individual
 - (b) Other conditions¹²⁰
- (3) Basophilic cells show Crooke's changes⁷⁷ which are characteristic for Cushing's syndrome but are not diagnostic^{29, 43, 49, 81, 90, 100, 120, 170, 175}
 - (a) These changes may be secondary to those in the adrenal cortex, including tumor^{15, 16}
 - (b) Significance of cellular changes is unknown^{61, 62, 170, 179, 181, 185, 185}
- (4) Crooke's changes in basophilic cells show⁹⁴
 - (a) Hyalinization
 - (b) Vacuolization (peripheral)
- c Cancer of basophilic cells rarely demonstrated²⁰
- d Amphophil cells (take acidophilic or basophilic stain) are found in^{116, 128}
 - (1) Cushing's syndrome
 - (2) Cases of virilism (cancer or hyperplasia of adrenal cortex)
- 2 Testes^{37, 38, 61, 88, 131}
 - a Seminiferous tubules
 - (1) Normal
 - (2) Atrophy (see Fig 97)
 - (3) Spermatozoa
 - (a) Normal or abnormal
 - (b) Numerous or few
 - b Interstitial tissue
 - (1) Normal
 - (2) Edematous
 - (3) Cells may be
 - (a) Normal
 - (b) Sparse
- 3 Hypothalamic nuclei may show atrophy⁷³

TABLE 8 AUTOPSY FINDINGS IN CASES COLLECTED BY THOMPSON AND EISENHARDT¹⁷⁸

ASSOCIATION WITH TUMOR	Number of Cases		
	TOTAL	EXAMINED	CROOKE'S CHANGES
Pituitary adenoma	60	39	35
Adrenal tumor	22	11	11
Thymic tumor	3	3	3
Arrhenoblastoma	1	1	1
No tumor of any gland	12	9	8
Total	98	63	58

XI PATHOLOGIC PHYSIOLOGY

(see 39 VI B)

A INTRODUCTION

- 1 The chief disturbance is considered to be one of adrenocortical function (hyperfunction and/or dysfunction)
- 2 Observations and deductions to date may be summarized as follows for clinical purposes

B BUFFALO OBESITY

- 1 Its rapid acquisition early in the disorder suggests hypothalamic hyperphagia although this phenomena may be present in cases due to adrenal tumor
- 2 Clinical observations on use of ACTH and cortisone demonstrate relation to excess 11 oxysteroid hormones of adrenal cortex^{58 59}

C PURPLISH STRIAE THINNING OF SKIN AND WASTING OF MUSCLES

- 1 Reifenstein (quoted by Albright¹) attributes these findings to failure of tissue synthesis due to antianabolic effect of "S" hormones a theory which has been questioned¹
- 2 Demonstrable carbohydrate changes in some cases of full blown Cushing's syndrome are not always present
- 3 Negative nitrogen balance (excess excretion of urinary nitrogen over amount taken in food) is seldom demonstrated but tissue wasting and osteoporosis are considered as evidence that this has occurred¹⁴⁶
- 4 Excess of urinary 17 ketosteroids reflect the "N" hormone metabolism ACTH increases 17 ketosteroid excretion suggesting relationship; however cortisone, an "S" hormone causes hair growth
- 5 While administration of testosterone may result in a greater positive nitrogen balance the same action occurs in conditions where N hormone is not lacking
- 6 The results of testosterone therapy may be attributed to offsetting the anti-anabolic effects of 'S' hormones as well as increasing the ratio of N/S thus creating a positive nitrogen balance
- 7 A defect in protein splitting or in conversion of fat or glucose into the proper

amino acids for tissue synthesis may be another cause of muscular wasting osteoporosis and other findings this effect, too, is essentially antianabolic

- In 1 case studied by Wilkins, the following was observed¹⁹⁵

- A negative nitrogen balance resulted with an intake of 97 Gm of nitrogen, equilibrium was then established on 15 Gm (cortin excretion an indication of 'S' hormones, was reduced on this low nitrogen intake)
- b When 97 Gm of nitrogen were given again, a positive balance occurred lasting for 30 or more days
- c This phenomena suggests that when the body was not overloaded with protein, its ability to produce amino acids for tissue synthesis was restored, possibly due to a decrease in the secretion of "S" hormones
- d In rats given adrenocorticotrophic hormone on the other hand, Ingle found the least loss of nitrogen was on a high protein diet and greatest on a high fat intake⁸⁰

D VASCULAR HYPERTENSION

- 1 Adrenocortical hormones
 - a There may be a direct effect on renal function by the hormones as shown by a decrease in⁸
 - (1) Blood flow
 - (2) Glomerular filtration
 - (3) Tubular secretion
 - b A relationship to the electrolytic changes which are occasionally found is possible^{8 50 90 127 198 199}
 - (1) Urinary loss of
 - (a) Potassium
 - (b) Chloride
 - (2) Blood
 - (a) Potassium—decreased
 - (b) Sodium—increased
 - (c) Carbon dioxide combining power—increased due to chloride loss^{90 127 198 199}
- 2 Desoxycorticosterone (DOCA) given to animals and men in sufficient amounts causes¹⁹⁰
 - a Hypertension
 - b Sodium retention
 - c Chloride retention
 - d Potassium loss
- 3 Vascular changes in Cushing's syn

drome are not exactly analogous to those produced by an excess of deoxy corticosterone (DOCA), although it is tempting to explain the hypertension as due to it or a similar steroid

- 4 A large intake of protein or salt may play a role in the production of hypertension when adrenal cortical hormones are increased

5 Pressor substances

- a Little is known about these in this disorder
- b Renin may be increased by the amorphous fraction of the adrenals

E CARBOHYDRATE METABOLISM

- 1 Diabetes in Cushing's syndrome is attributed to an excess of carbohydrate or 'S' hormones i.e., 11 oxysteroids, of the adrenal cortex
- 2 Varying degrees of insulin resistance are caused by these hormones through the retardation of glucose oxidation or utilization^{67-73 81 111 181 190}
- 3 Conversion of proteins to sugar is increased for energy purposes which may contribute to
 - a Hyperglycemia
 - b Glycosuria
- 4 Burning of fat is accelerated to save the proteins

F SUSCEPTIBILITY TO INFECTION

- 1 Protection against toxins infections or other forms of stress is lowered
- 2 Excess of S hormones natural or synthetic (Compounds A E and F) cause dissolution of¹⁹
 - a Lymphoid tissue (i.e. lymphocytes)
 - b Thymus
 - c Lymph nodes
- 3 The effects or results¹⁰¹
 - a Immune or protective globulins are released
 - b Circulating lymphocytes decreased
 - c Polymorphonuclear cells are increased
 - d Protection against toxins in the experimental animal
 - e In Cushing's syndrome these reservoirs are depleted rendering the patient more susceptible to noxious agents¹
 - f As Ingle points out this is a catabolic function not merely antianabolic⁸⁰

G HYPERTRICHOISIS

- 1 Is present in majority of cases
- 2 May be attributed to increased adrenal steroids (11 oxysteroids or 17 keto steroids) in an individual with hypertrichotic anlage

H GONADS

- 1 Both males and females (with rare exceptions) have a decreased function
- 2 Urinary gonadotropins are not decreased or increased, which is phenomenal considering the extent of change
- 3 Masculinization i.e., lowering of voice enlargement of clitoris is rarely present in the female cases
 - a If present one must postulate an increase in
 - (1) 'M' hormone
 - (2) Androgenic steroids
 - b Urinary 17 ketosteroids do not necessarily reflect the androgenicity of original adrenal steroids for they may be only metabolic end products

I OSTEOPOROSIS

- 1 Antianabolic effect of the excess (11 oxysteroids) hormones is probably responsible for
 - a Failure of laying down of bone matrix¹
 - b Nonutilization of
 - (1) Calcium
 - (2) Phosphorus
- 2 Although negative calcium balance has rarely been proved,¹ its existence is probable in earlier stages of the disease (nitrogen phosphorus and sulfur may also be affected)¹⁰⁰
- 3 Impairment of calcium and phosphorus absorption by gastro intestinal tract has been demonstrated⁸
 - a Calcium is retained when given intravenously^{80 140}
 - b Osteomalacia may also be present in this disorder
 - c Some believe that vitamin D facilitates calcium absorption^{59 140} (in this disease the problem is controversial)
 - d Testosterone is effective, whereas estrogens are not in creating positive calcium balance

J DISTURBANCE IN PSYCHE—No logical explanation can be offered for this

XII SYMPTOMATOLOGY

A NEUROMUSCULAR AND SENSORY

- 1 Headache
- 2 Asthenia
- 3 Fatigability
- 4 Backache
- 5 Pain in extremities
- 6 Insomnia
- 7 Vertigo
- 8 Convulsions ⁹¹
- 9 Unconsciousness
- 10 Mental depression
- 11 Eyes
 - a Dimness of vision
 - b Diplopia (transient)
 - c Pain around orbits

B CARDIOVASCULAR

- 1 Palpitation
- 2 Dyspnea
- 3 Angina

C GASTRO INTESTINAL

- 1 Polyphagia ^{85 10}
 - a Early—common complaint
 - b Later—decreased
- 2 Polydipsia ^{5 10}
- 3 Excessive weight gain
 - a Peculiar distribution
 - b Painful sometimes
- 4 Anorexia (due to uremia)

D GENITO URINARY

- 1 Amenorrhea (rare exceptions⁴)
- 2 Oligomenorrhea¹⁸
- 3 Impotence
- 4 Polyuria
- 5 Nocturia

E GENERAL—Hypertrichosis

XIII DIAGNOSIS

A HISTORY

- 1 Mental changes
- 2 Stature shrinks
- 3 Obesity
 - a Rapid accumulation
 - b Characteristic distribution at
 - (1) Face
 - (2) Trunk
- 4 Appetite
 - a Early in disorder—voracious
 - b Later—decreased
- 5 Libido lost
- 6 Amenorrhea in most cases regular catamenia ■ rare⁴

7 Fractures

8 Renal colic

B PHYSICAL EXAMINATION—Check for

- 1 Obesity—buffalo type
- 2 Plethora
- 3 Purplish striae
 - a Upper arms
 - b Axillae
 - c Abdomen
 - d Buttocks
 - e Thighs
 - f Absent
- 4 Hypertrichosis
- 5 Ocular fundi for retinal changes
- 6 Hypertension ■ usually present
- 7 Dorsal round back
- 8 Adrenal tumor
- 9 Testicular hypoplasia
- 10 Pelvic tumor, under anesthetic if necessary

C LABORATORY

- 1 Complete blood count
- 2 Blood chemical analyses
 - a Nonprotein nitrogen
 - b Cholesterol
 - Phosphorus
- 3 Tolerance tests
 - a Glucose
 - b Glucose insulin
 - c Insulin
- 4 Basal metabolic rate

D ROENTGENOLOGIC STUDIES

- 1 Skull
 - a Sellar size (see 2 \ IV H)
 - b Teeth
 - Osteoporosis
- 2 Spine
- 3 Chest
- 4 Abdomen
 - a Kidney stones
 - b Adrenal tumor
- 5 Pelvis
 - Air inflation (kidney area)

E DIAGNOSIS

- 1 The advanced case is easily recognized but early ones may present difficulties
- 2 If significant hypertension or amenorrhea is absent any 4 of the following 7 items should establish the diagnosis
 - Obesity (characteristic type)
 - b Loss of libido
 - c Amenorrhea
 - d Purplish striae

- e Hypertension
- f Osteoporosis
- g Diabetes
- 3 Exploration of the adrenals in most cases, even though no tumor can be demonstrated, may be required
- 4 Sometimes the tumor may be located in
 - a Sella turcica
 - b Chest
 - Pelvis

- b Striae may be
 - (1) Small
 - (2) Pink color
- c Hypertrichosis
- d Hypertension
- 2 The following are normal
 - a Hematology
 - b Blood chemical analyses
 - c Urinary hormone assays
 - d Bone texture

XIV DIFFERENTIAL DIAGNOSIS

A ADRENOGENITAL SYNDROME (see 42 VIII)

- 1 Females
 - a Precocious development in children
 - b Masculinization in adults
 - c Amenorrhea common but exceptions have been reported
- 2 Males
 - Condition is rare
 - b Spermatogenesis possible^{107 100}
- 3 Height age—increased
- 4 Fat distribution—normal
- 5 Striae—absent
- 6 Clitoris—usually prominent
- 7 Musculature—well developed⁷⁴
- 8 Blood chemical analyses—normal¹⁴¹
- 9 Bone
 - a Age—advanced
 - b Texture—normal

10 Adrenal tumor—may be found

B ARRHIENOBLASTOMA (see 73)

- 1 Body contours—masculine
- 2 Fat distribution—normal
- 3 Absence of
 - a Striae
 - b Ecchymosis
 - c Acne (rare exceptions)
- 4 Blood pressure—normal
- 5 Sexual development—precocious in young
- 6 Clitoris—always enlarged
- 7 Ovaries
 - a Normal—often
 - b Tumor—may be palpable
- 8 Blood chemical analyses—normal
- 9 Bone
 - a Age—advanced in young
 - b Texture—normal

C FAMILIAL BODY CONTOUR ('Cushingoid' in pattern, but without Cushing's disease)

- 1 Members of family may have
 - a Similar build

XV COMPLICATIONS SEQUELAE AND ASSOCIATED DISEASES

- A INFECTIONS—Marked susceptibility to any type
- B DIABETES MELLITUS
- C ORTHOPEDIC PROBLEMS—Fractures
 - 1 Spontaneous
 - 2 Compression
- D CARDIOVASCULAR
 - 1 Hypertensive changes
 - 2 Renal damage
- E PSYCHOSES
 - 1 Depressive state
 - 2 Confusion
 - 3 Suicidal tendency

XVI TREATMENT

A INTRODUCTION

- 1 No definite course of therapy can be advised which will ensure success
- 2 Listed below are the various treatments used for this most unusual disease
- 3 In general roentgen therapy over the pituitary should be tried especially if an enlarged sella is found
- 4 If, on the other hand, the condition is serious and with evidence of rapid progression the adrenal glands should be explored for
 - a Adenoma
 - b Carcinoma
- 5 Bilateral subtotal resection or total removal of one adrenal and subtotal excision of the other may be indicated
- 6 Spontaneous recovery is possible in mild cases

B ROENTGEN^{70 139 167}

- 1 Pituitary
 - a Indications
 - (1) Sella turcica enlargement
 - (2) Trial before exploration and/or adrenal resection

- (3) Absence of adrenal pathology especially adrenal carcinoma

b Procedure—see 13 IX

c Results (see Protocol 11 XXIV)

(1) From first series

- (a) Probably none
(b) Backache may be relieved
(c) Menses may return
(d) Acne may subside

(2) Subsequent series—final results variable¹ ■ 18 10 30 37 43 47

60 74 7 9 00 09 10 114 116 131
137 14 144 10 107 174 178 00 201

(3) Rotational therapy appears to be superior⁷⁸

2 Adrenal tumor or glands^{131 107}

a Indications

- (1) Nonresectable tumor
(2) Failure of other therapy

b Procedure and dosage depend on

(1) Tumor

- (a) Size
(b) Location

(2) Patient's condition

c Results—not known

C IMPLANTATIONS OF RADON SEEDS IN PITUITARY^{3 1 0 133}

1 Indications

- a If extensive surgery is contraindicated
b If roentgen therapy has been unsuccessful

2 Procedure

- a Transphenoidal route
b Dosage—1 millicurie/cc of normal tissue

3 Dangers

- a Infection
b Blind placement (radon seeds may not be inserted within tumor)

4 Result—some good reports³¹

D SURGICAL

1 Adrenals

■ Indications

(1) Unilateral

- (a) Removal of tumor^{0 1 90}
9 96 114 19

- (b) First step in 2 stage operation for bilateral resection

(2) Bilateral subtotal resection of normally appearing or hyperthrophied tissue with⁹

- (a) Uncontrolled disease

- (b) Bilateral hypertrophy

(3) Denervation—not known³¹

b Comments

- (1) An adrenal gland should not be removed until the presence of the other gland has been demonstrated^{78 168}

(2) Surgery is less hazardous

- Results—bilateral subtotal resection has not been proved yet ■ a sound therapeutic procedure ■ in spite of several reported cures, recurrence possible without pituitary irradiation (see Protocol 11 XXIII)⁸

2 Pituitary

a Indications

(1) Adrenals

- (a) Negative exploration

- (b) Unsuccessful partial resection

(2) Roentgen therapy failed to achieve results

(3) Sella is enlarged

(4) Generally not advisable^{8 108}

b Results

(1) Success rare

(2) Mortality high (see Protocol 11 XX)

E MISCELLANEOUS

1 Testosterone^{1 43 140 187 193}

■ Indications

(1) Late stages of disorder for

- (a) Weakness

- (b) Weight loss

(2) With roentgen therapy

- (a) For additional beneficial effects

- (b) If ■ failure

(3) Preoperatively for same purpose as (1)

(4) Postoperatively for

- (a) Adrenal tumor cases

- (b) Hastening recovery

b Dosage

(1) Methyltestosterone—oral or buccal 30 to 50 mg daily

(2) Testosterone propionate—intramuscular, average 25 mg daily to 3 times a week

c Results of both medications

(1) Increase in^{140 193}

- (a) Weight
- (b) Strength
- (c) 17 ketosteroids (may decrease with methyltestosterone¹⁴⁹)
- (2) Improvement in
 - (a) Diabetes
 - (b) Skin changes
- (3) Creatine
 - (a) Excretion — increased (can be prevented by testosterone propionate)
 - (b) Blood level—increased
- (4) Creatinine excretion^{43 193}
 - (a) Normal
 - (b) Increased slightly
- (5) Nitrogen balance may be increased, but less retention with continued usage^{1 3 43}
- (6) Calcium
 - (a) Decrease in^{1 3}
 - [1] Excretion
 - [2] Retention
 - (b) Balance (recalcification of bones)
 - [1] No change^{116 193}
 - [2] Increased^{1 3}
- (7) Phosphorus
 - (a) Balance—increased^{1 3}
 - (b) Retention — less marked with prolonged use¹¹⁰
- (8) Phosphatase (serum)—rise delayed (an index of bone matrix formation)^{1 3 43 130}

2 Insulin

- a Indications (see 85 XVI D 1)
 - (1) Diabetes
 - (2) Glycosuria which is uncontrollable with diet
- b Dosage
 - (1) Dependent on severity of condition
 - (2) Regulate as in any diabetic
 - (3) May require comparatively higher doses than in ordinary diabetes
- c Results—fairly good control

3 Diet

- a Low protein gradually increase amount^{113 196}
- b Limited sodium intake may be helpful³

4 Antihypertensive therapy

- a Hypertension may persist after the various treatments, probably due to renal damage⁷³
- b Low sodium diet, ammonium chloride or thiocyanates may be effective
- c Splanchnicectomy might be temporarily helpful

F OBSERVED EFFECTS OF OTHER ATTEMPTED THERAPY

- 1 Comment—the real value of the following is dubious potassium salts are the chief items which have shown corrective tendencies although producing little clinical change

2 Hormones

- a Estrogens^{3 11 43 44 47 50 179 184 193 149 150 153 169}

- (1) Dosage
 - (a) Variable
 - (b) Oral or intramuscular methods tried^{43 47 143}
- (2) Results
 - (a) Urinary excretion⁴³
 - [1] Creatine — slightly increased
 - [2] Creatinine—decreased
 - (b) No alteration in balance of^{1 3}
 - [1] Nitrogen (prolonged usage produces retention)
 - [2] Calcium
 - [3] Phosphorus
 - (c) Variable clinical improvement has been reported
 - [1] Subjective usually
 - [2] Little effect on
 - [a] Weight loss
 - [b] Plethora
 - [c] Hypertrichosis
 - [d] Blood pressure
 - [e] Genitalia
 - [f] Amenorrhea
 - (d) It has been given with testosterone without synergistic action^{1 3}

b Progesterone

- (1) Dosage—intramuscular 10 to 25 mg daily
- (2) Results^{1 3 44}
 - (a) Little effect on
 - [1] Cholesterol (plasma)
 - [2] Sugar curve

[3] Nitrogen balance

[4] Phosphorus balance

(b) Menstrual response unpredictable (see Protocol 11 XXIII)⁷⁸

3 Electrolyte balance

a Calcium

(1) Dosage

(a) Oral

[1] Lactate—10 to 30 Gm daily

[2] Chloride—10 to 30 Gm daily

(b) Intravenous—gluconate, 10 to 20 cc of 10 per cent solution

(2) Results

(a) Retention with intravenous administration^{59 140}

(b) Debatable if absorbed from^{1 15 9 140}

[1] Diet

[2] Oral medication

b Vitamin D

(1) Dosage—oral, 50 000 or more units daily

(2) Results—questionable retention of

(a) Calcium

(b) Phosphorus

c Potassium

(1) Acetate or chloride

(a) Dosage—oral 10 Gm daily

(b) Results^{8 117 120}

[1] Potassium level increased

[2] Hypochloremia corrected

[3] Alkalosis converted to normal

[4] Electrocardiogram may revert to normal

(2) Citrate

(a) Dosage—oral 10 Gm daily

(b) Results

[1] Potassium level increased

[2] Electrocardiogram changes may revert to normal⁵

G SUMMARY OF RESULTS (from adrenal surgery, prolonged roentgen therapy and/or

testosterone) (see Figs 100 and 101)^{21 22 121 167}

1 Unfavorable—disease may progress to fatal outcome

2 Favorable (if part or all the following take place)

a Increase in

(1) Strength

(2) Weight

b Color in striae may fade

c Ecchymotic tendency is lost

d Hypertrichosis decreases

e Blood pressure lowered

f Catamenia re established

g Libido may return (possibly)

h Bone changes

(1) Pain relieved

(2) Recalcification

(a) Healing of fractures

(b) Laying down of bone around compressed vertebrae

(c) Nucleus pulposus recompressed

i Hematology⁶⁹

(1) Decrease in

(a) Red blood cells

(b) Leukocytosis

(2) Increase in

(a) Lymphocytes⁶⁹

(b) Eosinophils⁷⁸

j Blood chemical analyses

(1) Decreased

(a) Sugar (see Chart 25)

(b) Nonprotein nitrogen

(2) Increased

(a) Calcium

(b) Phosphorus

(c) Phosphatase

k Balances—retention of

(1) Nitrogen

(2) Calcium

(3) Phosphorus

XVII PROGNOSIS

A INTRODUCTION—The following is based upon impressions as no large series of cases has been reported

B WITHOUT TREATMENT

1 Rapid fatal course, especially with

a Severe hypertension

b Coronary disease

c Malignancy

2 Spontaneous recovery is possible^{1 11}

C WITH TREATMENT

- 1 Surgery on
 - Pituitary
 - (1) Hazardous
 - (2) Ill advised
 - b Adrenal
 - (1) Reasonably favorable with availability of cortisone
 - (2) Cancer decreases chances for recovery
- 2 Roentgen therapy over pituitary—if response favorable, outlook is fair, especially if hypertension is not progressive¹⁰⁷
- 3 Other forms of management are usually palliative

XVIII CAUSES OF DEATH⁸⁰

A INFECTIONS

- 1 Pneumonia⁷⁸
- 2 Septicemia
- 3 Tuberculosis
- 4 Meningitis⁷⁸
- 5 Erysipelas

B MISCELLANEOUS

- 1 Heart failure
- 2 Uremia
- 3 Apoplexy (see Protocol 11 \XII)⁷⁸
- 4 Pulmonary edema
- 5 Pancreatitis (acute)
- 6 Gastric ulcer
- 7 Metastases⁷⁸
- 8 Postoperative complications
- 9 Suicide

CUSHING'S SYNDROME

Family history Cardiovascular disease

Past medical Negative

Chief complaints Backaches, headaches, weakness and obesity of 3 years duration

History of present illness Patient was well until 5 years before admission. At that time he was confined in a State Penitentiary where because of a prison riot, he was put into solitary confinement for 90 days on bread stew and water diet. During this period he gained weight rapidly and developed a peculiar fullness of his cheeks and purplish striae on the lower part of his abdomen. The adipose tissue seemed to be concentrated at the upper trunk, head and neck. He became weak, nervous and irritable with increased sweating, headaches, dyspnea, polydipsia, frequency and complete loss of libido. His hair remained the same. Three years later while in prison a thyroidectomy was attempted but only a pole ligation was done. Eight months later a subtotal thyroidectomy was performed following which he became sluggish both mentally and physically. He was so weak that ordinary duties could not be performed. Six months later he grew progressively worse. Headaches were very severe, numbness of legs, rib and girdle pain at level of fifth to seventh thoracic vertebrae. One year later he was given 30 intramuscular injections of pituitary extract without

PROTOCOL \X FIGS 95-97

effect. By that time he had so many pains that following the roentgen findings of generalized decalcification he was put in a body cast for 20 days. Thereafter he was bedridden for 10 months and lost 30 lbs. He was admitted to New Haven Hospital as a patient of Dr. Harvey Cushing.

Physical examination (At New Haven Hospital) Age 25, male, single. Weight 130 lbs. Height 68 in. Pulse 100 BP 220/160. Extremely rubicund, thick buccal pads, obesity of trunk, neck and thin extremities. Marked kyphosis and tenderness over ribs and dorsal spine. Visual fields normal. Heart enlarged to left, distant sounds of fair quality. Abdomen obese, no masses or tenderness. Deep purplish striae over thorax, abdomen and hips. Few ecchymotic areas over lower extremities and many congenital pigmented moles on his face. Edema of feet and ankles.

Laboratory data (At New Haven Hospital)

Urine normal. RBC 4,830,000. Hgb 95%. WBC 17,100. Differential: polymorphonuclears 87%, lymphocytes 10%, monocytes 2%, eosinophils 1%. Blood sugar 61 mg % NPN 30 mg % Serum total protein 5.67 Gm % Serum albumin 4.00 Gm % Serum globulin 1.67 Gm % Plasma cholesterol 209 mg % Serum sodium 131.4 mEq/l Serum potassium 5.4 mEq/l Serum calcium 11.58 mg % Serum phosphorus 3.26 mg % Serum lipid phosph

phorus 10.1 mg % Serum chlorides 99.5 mEq/l Serum carbon dioxide 72.2 vol % Serum total fatty acids 14.7 mEq/l Glucose tolerance test normal curve (may have been altered due to thyroidectomy) PSP 47% excretion in 30 min BMR minus 40% EKG normal Urinary hormone assays male sex hormone, 3 IU daily (normal adult male 25 IU), female sex hormone, 50 IU daily (normal adult male 25 IU)

Röntgenographic findings (At New Haven Hospital) Generalized decalcification, deformity of vertebral bodies of lower dorsal spine pathologic fractures of ribs, ischia and left pubis with callous formation Cardiac enlargement and widening of supra cardiac shadow Urograms were indeterminate

Treatment and progress Irradiation of pituitary, 5 series each consisting of 4 treatments on successive days Exploration of left adrenal—normal Patient was referred to the Lahey Clinic for exploration of the pituitary gland Physical examination the same except testicular atrophy was noted Operation by Dr Gilbert Horrax—no pituitary tissue removed Postoperatively the patient seemed to do very well for the first 4 days but then developed signs of intra-

cranial pressure and pneumococcal meningitis which caused his death

Postmortem findings Anatomic diagnoses purulent meningitis, healed fractures adipsity, cutaneous striae, aortic fibrosis peritoneal adhesions, testicular atrophy, pulmonary atelectasis, recent craniotomy with partial resection of right frontal lobe healed upper left quadrant incision Microscopic pituitary—high degree of hyalinization as described by Crooke, large cyst of the pars intermedia lined with ciliated epithelium, no basophilic adenoma Testes—tubules shrunken with increased basement membrane slight spermatogenic activity and very few mitoses present, interstitial tissue was edematous with rather rare shrunken (interstitial?) cells Adrenals—normal, no cytochemical studies made however

Summary Classical Cushing's syndrome associated with Crooke's changes in the pituitary The onset of the disorder was interesting and suggests the possibility of failure of the adaptation syndrome, with the patient remaining in the stage of counter shock and/or stage of resistance The hazards of surgery and susceptibility to infection is well illustrated Antibiotic therapy was not available then

CUSHING'S SYNDROME

Family history Negative

Past medical Patient was rejected by Army because of nervousness

Chief complaints Nervousness, exhaustion and variation in weight for 13 months

History of present illness Patient had been in good health until 13 months ago when he gained 40 lbs in 1 month due to an increased appetite and craving for sweets He became emotionally upset, exhausted, sleepy and lost about 26 lbs on a diet Because of a low BMR his physician gave him thyroid tablets (dosage not known) without improvement or effect on his weight During the next 6 to 8 months he developed mental sluggishness and depression, intolerance to cold, decreased libido and more marked fatigue Severe headache for 3 months, worse with sneezing cough

PROTOCOL XXI FIG 98

ing or in recumbent position Also low back pain and aches in his arms and legs

Physical examination Age 25 male, single Weight 147 lbs (usual weight 134, maximum 173) Height 70½ in BP 120/86 Florida, moon face and buffalo type of obesity (fat face neck and trunk with very thin extremities) Skin dry and coarse Deep purplish striae at axillae buttocks groins and thighs Eyelids puffy Marked dorsal round back Decrease in muscle mass of legs Slight weakness of his arms Hands mottled

Laboratory data Urine trace of sugar and albumin concentration 1.026 RBC 4,800-000 Hgb 15.6% WBC 11,400 Differential polymorphonuclears 75%, band forms 4% lymphocytes 11%, monocytes 10%, NPN 41 mg % Plasma protein 9 Gm %

Serum sodium 145.3 mEq/l Serum potassium 12.9 mg % Serum calcium 10.1 mg % Serum phosphorus 3.9 mg % Alkaline phosphatase 4.1 B U Carbon dioxide combining power (serum) 54 vol % Glucose tolerance test (blood sugar mg %) fasting, 63, 1 hr, 157 2 hrs 115, 3 hrs, 65 Repeated test fasting 76 1 hr, 189, 2 hrs 127 Glucose insulin tolerance test fasting 70 mg %, 1/2 hr, 111 mg %, 1 hr, 149 mg % 2 hrs, 174 mg % PSP (intravenous) 45% excretion in 30 min Sedimentation rate 2 mm/hr Urinary hormone assays FSH weak positive 17 letosteroids 39.2 mg/24 hrs

Röntgenographic findings Skull, chest and urograms normal Thoracic spine coarse trabeculation, calcium content compatible with hyperparathyroidism

Treatment Preoperative therapy testosterone, 50 mg daily for 1 week Benzedrine, 5 to 10 mg bid Exploratory operation excision of adrenal cortical tumor, size of orange Postoperative course uneventful Desoxycorticosterone 10 to 20 mg and cortical hormone, 30 cc for several days in decreasing doses Intravenous 10% glucose—2,000 cc daily for 4 days with added

penicillin 200 000 units daily

Progress Patient improved physically, but because of marked mental depression was transferred to the Psychopathic Hospital and then to Danvers State Hospital Four months later he died of bronchopneumonia

Postmortem findings (Danvers State Hospital) Autopsy revealed no unusual changes other than bronchopneumonia and fibrinous pleuritis Microscopic findings pituitary—glandular portion consisted mostly of chromophobes and eosinophilic cells, the nervous portion showed columns of basophilic cells invading the glandular part, Crooke's changes not noted Thyroid—atrophic, fibrous tissue replaced most of glandular tissue

Summary This case illustrates Cushing's syndrome due to adrenal cortical tumor, which was discovered only by exploration Serum sodium slightly increased, serum potassium low, and mild alkalosis yet no significant hypertension Essentially normal glucose tolerance but an equivocal glucose insulin tolerance curve Although bone pain, backache and appetite improved after removal of cortical tumor the severe mental depression remained the same

CUSHING'S SYNDROME

Family history Goiter

Past medical Enuresis until 10 to 12 years of age

Chief complaint Menstrual irregularity for 2 years

History of present illness Periods were regular until 2 years before admission She then had amenorrhea for 5 months After injections periods returned at irregular intervals (2 to 3 weeks early or late) Injections stopped 3 months previously amenorrhea since Patient gained about 14 lbs during present illness mostly around the head and the trunk Hair growth increased on face only Her cheeks seemed to be purplish in color Excessive offensive sweating BP (systolic) from 165 to over 200 Dyspnea on climbing stairs and swelling of her ankles at night Headaches variable occasional blurring of vision and tinnitus Nocturia for 3 to 4 months frequency and burning past few weeks

PROTOCOL XXII CHART 25

Physical examination Age 28, female, single Weight 140 lbs Height 63 1/4 in Pulse 80 BP 198/140 Obesity more marked around head and trunk extremities thin Cheeks are ruddy Facial hair increased Recent and old hemorrhages on lower left shin

Laboratory data Urine essentially negative concentration 1014 RBC 5 730,000 Hgb 109% WBC 15 400 Differential polymorphonuclears 65% band forms 13%, lymphocytes 12% monocytes 10% Hematocrit 50.5% Platelet count 510 000 Bleeding time 3 min Coagulation time 18 min Clot retraction about 35% Prothrombin 92% of normal Resistometer normal NPN 34 mg % Total protein 8.0 Gm % Serum albumin 4.5 Gm % Serum globulin 3.5 Gm % Serum calcium 10.5 mg % Serum phosphorus 2.1 mg % Serum alkaline phosphatase 4.4 B U Serum acid phosphatase 0.40 units Serum potassium 15.1 mg % Serum sodium 140.0

mEq/l Glucose tolerance test (blood sugar mg %) fasting, 81, $\frac{1}{2}$ hr, 196, 1 hr, 228, 2 hrs, 189 Glucose insulin tolerance test (blood sugar mg %) fasting, 107, $\frac{1}{2}$ hr, 185, 1 hr, 189, 2 hrs, 192, 3 hrs, 125 4 hrs, 83 Urea clearance 56% PSP total 42% Urinary hormone assays estrin negative 17 ketosteroids 10.5 mg (volume 1,300 cc) and 17.8 mg / 24 hrs (volume 2,850 cc)

Roentgenographic findings Skull—sella normal, osteoporosis, teeth normal Multiple old fractures of ribs lungs clear, heart normal Urograms normal Abdomen normal, except for hypertrophic changes at iliac crests Osteoporosis of lumbosacral spine and pelvis Old fracture of ascending and descending rami of the pubis with dense calcification There is some calcification in the region of the trochanteric bursa on the left

Treatment and progress Pelvic examination and exploration of adrenals—"normal" Irradiation of pituitary area 5 series of 6 treatments, 400 r each, over a period of 18 months During this time patient injured her leg which ulcerated and healed very slowly First menstrual period occurred 3 months after first series of roentgen therapy Ten months after beginning of roentgen treatment there was no significant change in repeated blood counts Serum phosphorus increased Blood pressures aver

aged around 150/100 No change in 17 ketosteroids, alpha steroids were 7.3 mg and beta steroids 12.2 mg / 24 hrs At the end of a year, glucose tolerance test showed improvement (blood sugar in mg %) fasting, 87, $\frac{1}{2}$ hr, 147, 1 hr, 135, 2 hrs, 107 No glycosuria Eighteen months after beginning of therapy, BP 180/120 Serum phosphorus 2.9 mg % Lymphocytes 19% Periods regular and patient feels in good health Weight 135 lbs One year later patient had cerebral apoplexy with hemiplegia

Summary This case illustrates the rather severe hypertension along with all other characteristic signs of Cushing's syndrome Adrenal exploration was negative Roentgen therapy caused resumption of normal catamenia and general improvement BP initially was 198/140 and 1 year later after several courses of roentgen therapy it was 150/102 Without further treatment, BP rose to 180/120 in 9 months Initially the serum phosphorus was 2.1 mg %, and at time of lowest blood pressure, 4.9 mg % During next 9 months, it was 2.9 and 3.1 mg % as BP rose again In view of failure to bring about permanent reduction in BP with irradiation, the question, in retrospect is whether bilateral resection of adrenals might not have accomplished this The answer is unknown, for this procedure is not always successful in this regard

CUSHING'S SYNDROME

Protocol XXIII

Figs 99 AND 100 CHART 137

Family history Father died of cardiovascular disease Brother died of hypertension, under age of 30

Chief complaint Weakness weight gain, hirsutism, fullness of face, headache irregular scant periods and finally amenorrhea

History of present illness Five years previous to admission, patient noted gradual onset of chief complaints Weight gain, 42 lbs For 6 weeks, nocturnal dyspnea Edema of ankles for 2 weeks Pain in low back and legs

Physical examination Age 26, female Weight 137 lbs Height 59 in Pulse 88 BP 190/130 Moon face, hirsute and ruddy com

plexion Numerous purplish striae Fundi not remarkable Gallop rhythm

Laboratory data Urine albumin 0, sugar 0, specific gravity 1.013 sedimentation—few WBC RBC 5,300,000 Hgb 16.5 Gm (average) WBC 8,950 Differential polymorphonuclears 73% lymphocytes 13% monocytes 9% Platelets 208,000 Capillary fragility normal NPN 48 mg % Serum uric acid 5.4 mg % Serum phosphorus 3.3 mg % Plasma cholesterol 228 mg % Serum calcium 10.7 mg % Serum alkaline phosphatase 3.6 BU Urea clearance 49% of normal Urinary hormone assays FSH—weak positive estrin—Grade I, 17 keto

steroids 16.8 mg/24 hrs Bone marrow—increased fat, otherwise normal After roentgen therapy (unimproved), serum potassium 14.2 mg % and chlorides 100 mEq/l Glucose tolerance test (blood sugar mg %) fasting 86, ½ hr, 243, 1 hr, 264 2 hrs 218 Etamox test marked response with no blood pressure in sitting position EKG—marked LAD and inversion T₁ and T

Roentgenographic findings Skull—osteoporosis, posterior clinoids thin, depression of sella into floor of sphenoid sinus, lateral contour area of sella was 150 sq mm, loss of lamina dura Pyelograms—normal, left kidney lower than right Chest—fracture of several ribs with callous formation Legs—osteoporosis, numerous growth lines

Treatment Patient received 2 series roentgen therapy—total 2,000 r over pituitary No change in condition Hemorrhagic ulcer on skin Hospitalized Bilateral partial adrenalectomy attempted, cardiac arrest, necessitating massaging of the heart recovery Three weeks later uneventful bilateral hemiadenectomy (Dr R B Cattell) Adrenals appeared hyperplastic however,

weight of removed tissue was 4.3 Gm Microscopic—normal adrenal tissue

Progress Two years after operation general condition satisfactory, except for blood pressure which after a few months returned to values around 180/140 when she did not take potassium thiocyanate, otherwise it was down to 140/100 Gallop rhythm and nocturnal dyspnea did not return Back or leg pain relieved No ecchymotic tendency Menstruation followed when given progesterone sublingually for 5 day periods Total eosinophil count was 100/cu mm 1 year after operation and declined gradually to 25/cu mm 1 year later Lymphocytes 16%

Comment This case illustrates persistent hypertension when symptomatically and otherwise there has been general improvement The hypertensive family anlage may be a predisposing factor Other treatments as testosterone, low salt and high protein diet ammonium chloride may have contributed a little to her well being Potassium thiocyanate 6 to 9 gr a day, had the most marked effect on her blood pressure

CUSHING'S DISEASE WITH AN ENLARGED SELLA Protocol XXIV FIG 102

Family history Negative

Past medical Married 11 years No children

Husband alcoholic

Chief complaint Bloating

History of present illness Seven months before admission patient noted frontal headaches and slight gain in weight (Weighted 86 lbs at marriage) Six weeks before entry she had marked bloating puffiness of eyes and blurred vision Headaches ceased with onset of edema Hypertension discovered 3 weeks before admission Given an injection which caused marked diuresis Amenorrhea for 2 months

Physical examination Age 28 female married Weight 132 lbs Height 56 in BP 145/90 160/120 Buffalo type of obesity pig eyed and moon face Purple striae on abdomen Acneform and seborrheic eruptions near hair line chest and back Hirsutism of face and chin

Laboratory data Urine albumin 1 plus sugar trace specific gravity 1.003 RBC

5,420,000 Hgb 16.8 Gm WBC 5,200 Hematocrit 52% Serum calcium 9.7 mg % Serum phosphorus 3.1 mg % BMR plus 2% Sedimentation rate 57 mm/hr

GLUCOSE TOLERANCE TEST

Hour	Serum Inorganic		Urine Sugar
	Blood Sugar mg %	Phosphorus mg %	
0	117	4.0	0
½	235	4.0	Trace
2	233	2.5	6.3%
3	267	2.9	6.0%

Roentgenographic findings Skull—thin cranial vault no decalcification sella 152 sq mm floor of fossa destroyed and right posterior clinoid process Pelvis—no osteoporosis Arteriosclerosis of pelvic vessels No displacement of kidneys

Treatment Irradiation 200 r to each tem

poral region daily Total of 2,000 r to each side

Progress Four months later Return of menstrual periods Normal libido No bloating Feels well Weight 119 lbs without diet BP 120/100 standing 120/118 Skin eruption cleared Striae fading RBC 4,800 000 Hgb 14.3 Gm WBC 8,000 Hematocrit 39% Total eosinophilic count 131/cu mm Fasting blood sugar 82 mg % Fasting serum phosphorus 4.0 mg % Sedimentation rate 70 mm/hr

tions cleared Striae fading RBC 4,800 000 Hgb 14.3 Gm WBC 8,000 Hematocrit 39% Total eosinophilic count 131/cu mm Fasting blood sugar 82 mg % Fasting serum phosphorus 4.0 mg % Sedimentation rate 70 mm/hr

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FIG 95 CUSHING'S SYNDROME (See Protocol 11 \ \ Figs 96 and 99) Bedridden because of extreme weakness and pain in back. Note striae of trunk, normal or excess hair, adequate beard, buffalo obesity. Scars from adrenal exploration. This man's disorder began during solitary confinement when he developed great thirst, gain in weight and purplish striae on a diet of bread, water and an occasional stew. Is this the alarm reaction without counterreaction? (See Adaptation Syndrome)



FIG 96 CUSHING'S SYNDROME (See Protocol 11 \ \ Figs 95-97) Striae on legs of patient shown above

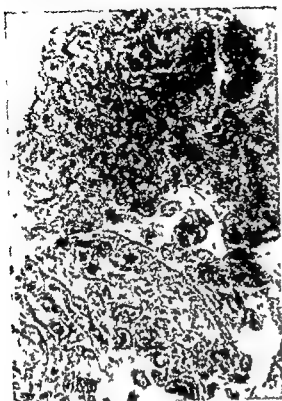


FIG 9, TESTICULAR ATROPHY IN CUSHING'S SYNDROME (See Protocol 11 \ \ Figs 95-96)



FIG 98 CUSHING'S SYNDROME (See Protocol 11 \ \ \ \) Weakness rapid increase in weight and mental depression for 1 year Buffalo obesity Striae on thighs buttocks axillae and groins Testes small Adequate beard Benign adrenocortical tumor removed without improvement



FIG 95 CUSHING'S SYNDROME (See Protocol 11 \ \ Figs 96 and 99) Bedridden because of extreme weakness and pain in back. Note striae of trunk, normal or excess hair, adequate beard, buffalo obesity. Scars from adrenal exploration. This man's disorder began during solitary confinement when he developed great thirst, gain in weight and purplish striae on a diet of bread, water and an occasional stew. Is this the alarm reaction without counterreaction? (See Adaptation Syndrome)



FIG 96 CUSHING'S SYNDROME (See Protocol 11 \ \ Figs 95-97) Striae on legs of patient shown above

FIG 100 CUSHING'S SYNDROME (See Protocol 11 XVIII Fig 99 Chart 13.) (Right) Advanced case showing the moon face the typical plethoric obesity and purplish striae. Five years before admission patient noted an increase in weight (42 lbs) and change in body contour. Hirsutism and headaches. Irregular menstruation was followed by amenorrhea. Weakness and pains in legs ensued. Finally paroxysmal nocturnal dyspnea and ankle edema. BP 190/130. Gallop rhythm. Urine negative. Hgb 15, Gm. \P\ 43 mg. % Sella enlarged unilaterally with depression into floor. Vault osteoporotic with loss of periodontal membranes. Several rib fractures. Osteoporosis of all bones. Fasting blood sugar 34 mg. % Serum calcium 10.5 mg. % Serum phosphorus 2.2 mg. % Alkaline phosphatase 3.6 B. u. Urograms negative. Little effect from 2 courses of roentgenotherapy. Bilateral subtotal adrenalectomy performed. Temporary fall in blood pressure. General improvement. Loss of back pain. Ecchymoses of legs. Nocturnal dyspnea. Menstrual periods with oral progesterone therapy. BP maintained at lower levels with sedatives or potassium thiocyanate. Patient has no complaints 2 years after operation.

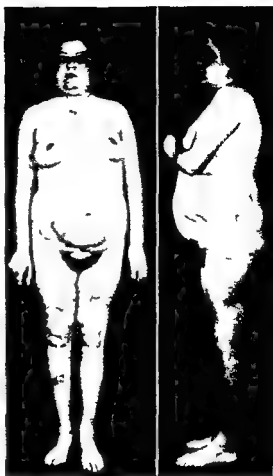


FIG 100 CUSHING'S SYNDROME Continued Facial appearance before therapy and two years later



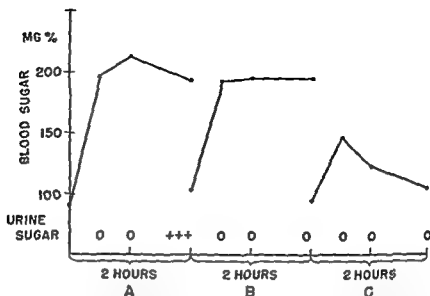


CHART 23 ORAL GLUCOSE TOLERANCE AND GLUCOSE INSULIN TOLERANCE TESTS IN CUSHING'S DISEASE (See Protocol 11 \\\II) (A) Glucose tolerance test showing diabetic curve (B) Insulin glucose tolerance test showing essentially no effect on hyperglycemia No glycosuria suggesting that insulin has raised renal threshold (increased phosphorylation) (C) Normal glucose tolerance test 1 year later Roentgen ray treatments over pituitary with improvement



FIG 99 CUSHING'S SYNDROME (See Protocol 11 \\\III Fig 100 Chart 137) (Left) Pathologic fractures of ribs with callous formation (Right) Healed 4 months later These films show that despite osteoporosis local injury is sufficient to overcome antianabolic or catabolic influences in this disorder

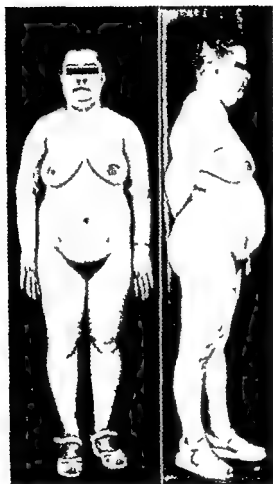


FIG 102 CUSHING'S SYNDROME (See Protocol 11 XXIV) Re-establishment of menstruation and loss of weight without dieting after roentgen therapy



FIG 101 CUSHING'S SYNDROME—CHANGE IN FACIAL CONTOUR AFTER THERAPY *Chief complaints* Swelling of face and ankles for 5 months. Facial hair growth and weakness of her legs. *History of present illness* Patient developed a craving for salt and crackers. Ammonium chloride was administered without benefit. Menstrual periods were regular but decreased gradually in amount. Ecchymoses occurred on her arms with slight trauma. Weight 157 lbs a gain of 7 lbs. *Physical examination* Age 47 female. Moon face. Ecchymotic spots on arms and face. No striae. BP 210/120. Pitting edema of ankles. Marked muscular weakness patient has to pull herself up with her arms from a sitting position. *Laboratory data* RBC 4.8 million Hgb 12.4 Gm WBC 9700. Differential polymorphonuclears 84%, lymphocytes 12.5% and monocytes 3.5%. Total eosinophilic count zero. Resistometer normal. Platelets normal. Glucose tolerance test fasting 121 mg % $\frac{1}{2}$ hr 263 mg %, 2 hrs 320 mg %, 3 hrs 182 mg %. Urine sugar 4% at 3 hrs. 17 ketosteroids 17.5 mg/24 hrs. *Roentgenographic findings* Normal skull pelvis and pyelograms. *Treatment* Roentgen therapy—4 000 r over 2 portals (skin dose).

PROGRESS BY

MONTHS

- 2 Testosterone 10 to 50 mg 3 times a week. Adrenal exploration. Right adrenal slightly increased in size 70% resected. Left adrenal 90% resected.
- 4 Slight general improvement. 17 ketosteroids 36 mg/24 hrs.
- 6 No improvement. Differential polymorphonuclears 59% lymphocytes 19.5% monocytes 11% and band forms 6.5%. Total eosinophilic count zero.
- 7 Rotational roentgen therapy 4 500 r (tumor dose).
- 9 Less hunger. Questionable improvement.
- 11 Improvement began shortly after last visit. Muscular weakness is less severe. No further ecchymoses. Edema is not evident. Swelling of face subsiding. Hair growth becoming blacker. BP 180/100. Differential polymorphonuclears 63% lymphocytes 32% monocytes 32% and eosinophils 1%. Serum potassium 21.2 mg % Serum sodium 47.8 mEq/l.
- 13 133 lbs BP 160/100. Rounded faces gone. No edema.
- 14 Weakness of legs slight. No excess hair on face. BP 170/100. Glucose tolerance test fasting 87 mg % $\frac{1}{2}$ hr 141 mg % 2 hrs 131 mg % 3 hrs 125 mg % No glycosuria. Total eosinophilic count 92/cu mm.

B HEMOGLOBIN		
1 Range (all cases)		68 to 104 per cent
2 Average		85 per cent
C BLOOD SUGAR (fasting)		
1 Range (49 cases)		73 to 137 mg %
2 Average		84.9 mg %
D PLASMA CHOLESTEROL		
1 Range (74 cases)		133 to 398 mg %
3 cases		Over 250 mg %
2 Average		230 mg %
E BASAL METABOLIC RATE		
1 Range (86 cases)		Plus 5 to minus 40 per cent
2 cases		Above minus 10 per cent
2 Average		Minus 20 per cent

TABLE 9 RESULTS OF TREATMENT OF 144 CASES OF CHROMOPHOBE TUMOR¹

NO OF CASES	VISION BEFORE TREATMENT	SURGICAL AND ROENTGEN THERAPY	ROENT GEN THERAPY (ONLY)*	HORMONAL THERAPY	VISION AFTER TREATMENT	RESULTS OF TREATMENT
55	Treatment because of other symptoms rather than eye changes	1	12	9	Normal	Improved Unchanged Worse
16	Incapacitated by loss of sight	7	5	4	Very good	Marked improvement post operatively able to resume normal occupation
41	Impaired but patient still at work	8	20	13	Good	Improved after operation able to continue normal occupation
15	Incapacitated by loss of sight	3	9	1	Moderate	Slight operative improvement sufficient only for intermittent work or new occupation
9	Impaired but patient still at work	2	4	3	Satisfactory	No change after operation continued with normal occupation
3	Incapacitated by loss of sight	2	1		Poor	No change after operation no useful vision remained for work or reading
5	Various degrees of impairment	2	2	1	Progressive deterioration	Fading vision or other disabling symptoms continued to progress or new complaints developed within 6 months
3						No follow up
17	Various degrees of impairment	10	6	1		Postoperative deaths and one during roentgen therapy
144	Total	36	49	47	9	

* Hormonal therapy used when indicated

SECTION 12

CHROMOPHOBE TUMORS

(Analysis of 144 cases presumed or verified¹)

I PHYSICAL STATUS

		PER CENT
A SEX		
1 Males	73	
2 Females	71	
II AGE—Onset (approximate)		
	PER CENT	
1 13 to 19	11	
2 20 to 29	20	
3 30 to 59	60	
4 60 and over	9	
C WEIGHT		
1 Normal, no change	43	
2 Under	26	
3 Over	30	
D VISUAL CHANGES		
1 Optic atrophy (unilateral or bilateral)		81
2 Field defects		82
3 Acuity absent or reduced, one or both eyes		76.7
F AXILLARY AND PUBIC HAIR		
1 Normal		18
2 Decreased or absent		72
F BLOOD PRESSURE		
1 Range	80/50 to 230/100	
2 Average	118/72	
3 Systolic		
		PER CENT
a Below 120		39
b Below 100		8
c Above 145		13

II SYMPTOMATOLOGY

A SEXUAL LIBIDO		
1 Absent or decreased (50% under 40 years of age)	72 per cent of those questioned	
2 Increased	Less than 1 per cent (1 case)	
B AMENORRHEA (before age of 42)		
	57 per cent	
C MISCELLANEOUS		
1 Visual changes (as a complaint)	CASES	PER CENT
a Blurred	74	80
b Halved vision	29	
c Blind one eye	12	
d Blind, both eyes	2	
e Diplopia	15	
f Unilateral ptosis	3	
g Strabismus	1	
h Scotoma	2	
2 Headaches		21
3 Fatigability		14
4 Drowsiness		7.1
5 Pallor		7
6 Polydipsia less than		1 (1 case)
7 Numerous other complaints		

III LABORATORY DATA

A RED BLOOD CELLS		
1 Range (all cases)	3.4 to 5.5 million	
2 Average	4.4 million	

SECTION 13

SUMMARY ON PITUITARY TUMORS

I TUMORS IN THE REGION OF THE SELLA

- A ADENOMA
- B CRANIOPHARYNGIOMA
- C SUPRASellar MENINGIOMA
- D ANEURYSM
- E GLIOMA OF THE OPTIC CHIASMA
- F CHOLESTEATOMA
- G ASTROCYTOMA
- H CHORDOMA

II INCIDENCE

	PER CENT
A ADENOMA	28 (of all intra cranial tumors)
1 Chromophobe	70
2 Chromophil	19.4
3 Mixed	10.6
B CRANIOPHARYNGIOMA	4.5 (of all intra cranial tumors)
C ALL OTHERS LESS THAN	10

III AGE¹

- A ADENOMAS
 - 1 Range—15 to 65 years
 - 2 Peak at 35 years
- B CRANIOPHARYNGIOMA
 - 1 Range—2 to 63 years
 - 2 Peak around 15 years

IV DIFFERENTIATION OF ADENOMAS FROM OTHER SELLAR TUMORS^{10 11}

- A MENINGIOMA
 - 1 Adults usually
 - 2 Glandular signs and symptoms are not marked
 - 3 Sella
 - a Normal
 - b Deformed slightly with some evidence of proliferation at the tuberculum sellae

- 4 Visual fields
 - a Optic atrophy
 - b Bitemporal field defects are often much more advanced in one eye
- 5 Ventriculography—see 2 VIII F 6
- B CRANIOPHARYNGIOMA (see 3 IV)
 - 1 Most frequent in children but do occur in adults
 - 2 Sella
 - a Calcification above it in 70 to 80 per cent
 - b Enlarged
 - c Deformed
 - d Not symmetrically ballooned
 - 3 Tumor often protrudes posteriorly behind the chiasma into the third ventricle producing hydrocephalus
 - 4 Choked disks sometimes instead of optic atrophy
 - 5 Ventriculography—see 2 VIII F 6
- C ANEURYSM (see Fig 104)
 - 1 Glandular symptoms are lacking in most cases (see Protocol 7 VII)
 - 2 Sella
 - a Enlarged as in adenomas
 - b Deformed
 - c Sharpening or elevation of one anterior clinoid
 - d Characteristic crescentic shadow may be present on the roentgenogram
 - 3 Visual fields have a tendency to bitemporal defects
 - a Homonymous
 - b Incomplete
 - 4 Arteriograms (roentgenograms taken during injection of thorotrast into the common carotid) give positive diagnosis (see 2 VIII F 5)
- D RARE TUMORS (gliomas of the optic chiasm or nerves, cholesteatomas and others)
 - 1 Glandular manifestations are not present usually
 - 2 Sellar expansion is not seen as in adenomas
 - 3 Visual fields
 - a Bizarre
 - b Hemianopsias (not clear-cut)

IV THERAPEUTIC RESULTS

A SUMMARY

1 Follow up of 26 cases after 10 years or more¹

a Treatment	CASES
(1) Operation	23
Postoperative deaths	3
(2) Roentgen radiation	2
(3) None	1
b Vision	
(1) Normal or improved	19
(2) Worse	2
(3) Blind	2

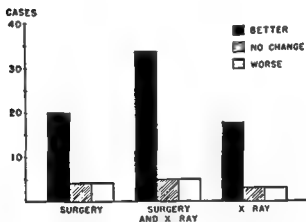
2 Follow up of 124 cases (of 144¹, Chart 26 and Table 9) for 1 to 25 years

a Treatment	CASES
(1) Operation (including secondary operations)	36
Postoperative deaths	16
(2) Operation and roentgen radiation	49
(3) Roentgen radiation (1 death)	47
(4) Hormonal	9
b Vision—see Table 9 and Chart 26	

REFERENCE

- 1 Horrax G H Hare H F, Younghusband O and Hurthall L M Unpublished data

RESULT OF TREATMENT ON VISION



RESULT OF TREATMENT IN PATIENTS WITHOUT VISUAL CHANGE

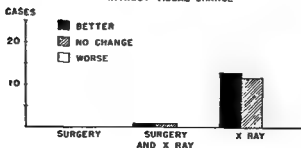


CHART 26 SUMMARY OF THERAPEUTIC RESULTS IN PATIENTS WITH CHROMOPHOBE TUMOR (presumed or verified) (Younghusband O Hurthall L M Horrax G H and Hare H F Unpublished data)

to pituitary disease with acromegaly or gigantism not listed elsewhere)

- a Hypertrichosis
- b Pigmentation
- c Skin fibromata
- d Asthenia
- e Parasthesias
- f Blood pressure is low
- g Lactation persists
- h Libido decreased
- i Spontaneous rupture of tumor
- j Sexual characteristics may return without treatment

VII SURGICAL TREATMENT

A OPERATIONS FOR PITUITARY TUMORS OR CYSTS^{1,2,3,4,5,6,7,8,9,10,11}

- 1 Transfrontal approach (see Figs 107-110)
 - a A relatively small osteoplastic bone flap just above the right frontal sinus is used to avoid danger of infection from the latter (usually easier for right handed surgeon)
 - b The scalp incision, almost wholly within the hairline is
 - (1) Curvilinear
 - (2) Reflected forward
 - c The dura is retracted from the inner surface of the skull and orbital plate down to the sphenoidal ridge where it is attached
 - d The dural incision is carried forward and upward over the tip of the frontal lobe for maximum retraction with the least possible injury
 - e An abundance of fluid is practically always obtained by a slight nick into the subarachnoid space
 - (1) It is usually unnecessary to tap the lateral ventricle
 - (2) A ventricular needle may be inserted perpendicularly through the lateral posterior portion of the field
 - f A smooth flat spatula or lighted retractor is now used to draw back the frontal lobe which is protected over its upper portion by the dura
 - g The upper surface of the adenoma is immediately recognized protruding

just medial to the right optic nerve in the space between the chiasm and the tuberculum sellae

- h The nerve and the surface of growth are covered by the arachnoid which must be carefully incised to allow further retraction of the frontal lobe back to the chiasm and medially to the left optic nerve
 - i The nerves may be so widened and flattened by compression that they can scarcely be distinguished from the actual surface of growth
 - j A needle attached to a syringe is inserted into the tumor for two purposes to
 - (1) Withdraw cystic contents if present
 - (2) Determine if an aneurysm is there (withdrawal of fresh arterial blood would establish the fact)
 - (a) The needle is removed if an aneurysm is found
 - (b) Entrance point of needle is sealed by
 - [1] A piece of muscle from the temporal region held securely in position there
 - [2] Gelfoam
- 2 Transphenoidal approach⁸
 - a Indication—tumors not accessible by transfrontal route
 - b This method is
 - (1) Used rarely
 - (2) Not recommended except in the hands of those who are accustomed to this operation
 - 3 Procedures for specific types
 - a Solid adenoma
 - (1) Circular opening is made in the capsule
 - (2) Soft reddish gray tissue is spooned or sucked out as completely as possible
 - (3) Capsule is gently separated and pulled away from the optic nerves and chiasm
 - (4) Portion lying above the sella turcica is
 - (a) Excised

V MIXED TYPES (see Figs 103, 105 and 106)

A CLINICAL MANIFESTATIONS

- 1 Hyperpituitarism to hypopituitarism—beginning with signs of chromophil tumor (hyperpituitarism) and ending with findings of a chromophobe tumor (hypopituitarism)
- 2 Hypopituitarism to hyperpituitarism
 - a Onset with signs of chromophobe tumor and terminating with findings of a chromophil type
 - b Dwarfism to gigantism
- 3 Simultaneous hyperpituitarism and hypopituitarism
 - a Tumor may be initially composed of both chromophils and chromophobes with variations in basophilic cells
 - b This may be the reason in some cases for conflicting evidence as regards the establishment of hypopituitarism and hyperpituitarism
 - c Hypopituitarism may accompany¹
 - (1) Urinary gonadotropins in excess
 - (2) Hot flashes in menopausal women
 - d Growing pituitary giants with hypersecretion of growth hormone may also have hypopituitarism

VI SYMPTOMATOLOGY

A TUMOR EXPANSION (see Fig 24 p 109)

- 1 Headache
 - a Acromegaly particularly
 - b Location
 - (1) Frontal
 - (2) Bitemporal
 - c Vague
 - d Persistent
- 2 Visual changes
 - a Chromophobic type especially
 - b Fields restricted
 - c Hemianopsia
 - (1) Unilateral
 - (2) Bilateral
- 3 Drowsiness
- 4 Polydipsia
- 5 Unicentric attacks
- 6 Mental effects
 - a Aberrations
 - b Confusion
 - c Depression psychosis

7 Lacrimation—absent (rare)⁹

8 Gait may be affected

B FROM DEFICIENT PITUITARY SECRETION

- 1 Before puberty
 - a Growth retarded
 - b Sexual development delayed
 - c Mentally alert, except when tumor
 - d Pallor
 - e Anemia
- 2 After puberty
 - a Libido decreased
 - b Amenorrhea
 - c Hair decreases
 - d Weight gain (see Fig 103)
 - e Pallor in some
 - f Fatigue
 - g Lethargy
 - h Somnolence
- 3 Simmonds' disease (complaints as in anorexia nervosa)
 - a Vomiting
 - b Weight loss
 - c Emaciation
 - d Amenorrhea
- 4 Thyroid deficiency (symptoms like myxedema)
 - a Drowsiness
 - b Coldness
 - c Skin—dry
 - d Pulse—slow
 - e Patient may also have adrenal symptoms

5 Adrenal insufficiency (symptoms like in Addison's disease)

- a Weakness
 - b Weight loss
 - c Anorexia
 - d Hypoglycemic attacks
- 6 General (signs or symptoms related to hypopituitarism not mentioned elsewhere)
- a Beard scant
 - b Hair texture changes
 - c Weight gain

C FROM EXCESS PITUITARY SECRETION

- 1 Increase in
 - a Height
 - b Acral parts
- 2 Menses
 - a Amenorrhea
 - b Oligomenorrhea
- 3 General (signs and symptoms related

- b Dosage—intramuscular, 25 mg daily for 4 to 5 days (or longer) before surgery
- 4 Protein equivalent to 10 Gm of nitrogen
 - a Dosage
 - (1) Orally
 - (2) Hydrolysates
 - b Result—extent of utilization is questionable
- 5 Salt—dosage
 - a Oral—5 to 10 Gm
 - b Intravenous—1,000 to 2,000 cc daily
- 6 Potassium salts
 - a Indication—to adjust electrolyte balance, rarely required
 - b Dosage
 - (1) Oral (citrate 20% solution)—4 to 8 cc in fruit juice daily
 - (2) Intravenous (chloride)—3 to 4 Gm with intravenous fluids daily

C POSTOPERATIVE COMPLICATIONS

- 1 Intracranial complications
 - a Surgical measures may be necessary
 - b Lumbar puncture for increased spinal fluid pressure
- 2 Hyperthermia
 - a Penicillin
 - b Cold packs
- 3 Acute adrenal insufficiency—dosage of medications
 - a Adrenocorticotrophic hormone—intramuscular 25 to 200 mg daily
 - b Cortisone—oral or intramuscular, 50 to 100 mg daily
 - c Adrenocortical hormone (aqueous)—subcutaneous 10 to 30 cc daily, gradually reduce
 - d Desoxycorticosterone—parenteral 5 mg daily
 - e Glucose—intravenous, 5 per cent solution in saline 2,000 cc daily
- 4 Potassium deficiency—see above—B 7
- 5 Sodium retention
 - a Ammonium chloride—oral 15 gr q: d
 - b Glucose intravenously
- 6 Diabetes insipidus—may be transient (see 8 XVI)

IX ROENTGEN THERAPY^a

A TECHNIC

- 1 Factors
 - a K V P 200
 - b Distance 50 or 70 cm
 - c Filter 1 mm copper and 1 mm aluminum
 - d Ma 20
 - e Portals 5 cm—temporal directing beam at sella turcica
- 2 Dosage ($r \approx$ roentgen units)
 - a Daily dose
 - (1) 300 to 400 r (measured in air)
 - (2) Give 1 treatment daily
 - (3) Alternate parts every other day
 - b Total dose
 - (1) First series—8 to 12 treatments
 - (2) 1,200 to 1,800 r to each portal
 - c Tumor dose—1,200 to 1,800 r approximately
- 3 Treatment—may be repeated every 2 months depending on indications
- 4 Rotational therapy permits larger doses to be given without skin damage (method by Hare and Trumpf^b)
 - a Dose—up to 4,500 r in 18 days
 - b Method of choice in
 - (1) Active acromegaly
 - (2) Cushing's syndrome without adrenal tumor

B COMPLICATIONS

- 1 Immediate
 - a Development after 1,200 r or more in 300 to 400 r daily
 - b Radiation sickness denoted by
 - (1) Nausea
 - (2) Vomiting
 - (3) Severe headache from edema occasionally
 - c Symptoms disappear within 48 hrs
- 2 Intermediate
 - a Development—3 weeks following above radiation therapy
 - b Hair
 - (1) Depilation in treated area
 - (2) Regrowth may take place in approximately 2 months time
 - c Skin may show variable degrees of erythema to blistering

- (b) Shriveled by electrocoagulation
- b Cystic adenoma
 - (1) Large incision made in capsule
 - (2) Liquid contents removed
 - (3) Solid portion excavated by
 - (a) Long pituitary scoops
 - (b) Strong suction
- c Chromophobe tumors, sometimes cause internal hydrocephalus by their growth upward and back of the chiasm into the region of the third ventricle
 - (1) These are the most dangerous and difficult surgical tumors
 - (2) Operative mortality varies from 3 to 5 per cent (30 to 40% reported in the literature)
 - (3) It may be necessary to
 - (a) Sacrifice one optic nerve
 - (b) Resect a portion of the frontal lobe
- d Extensive growth behind and above one chiasm or any extension under either temporal lobe (see Fig 111 and 112)
 - (1) Capsule may be
 - (a) Grasped by alligator forceps and drawn forward
 - (b) Excised above the sella in smaller tumors
 - (c) Left undisturbed at intrasellar portion with flattened pituitary body below it
 - (2) Tumor must be evacuated completely as possible with
 - (a) Suction
 - (b) Scooping
 - (3) Portion of cortex (temporal) may be
 - (a) Excised partially
 - (b) Transected
- 4 Comment
 - a Pituitary adenomas
 - (1) Solid usually
 - (2) Contents are variable
 - (a) Extremely soft
 - (b) Degenerated material
 - (c) Firm fibrous growth (difficult to remove)
 - b Complete evacuation of adenomas should be attempted
 - (1) This may be hazardous

- (2) Great care must be taken in freeing the tumor when it extends laterally into the region of the carotid arteries

B RESULTS—see 12 IV and 13 VIII

VIII PREOPERATIVE AND POST OPERATIVE MANAGEMENT

- A EVALUATION OF PATIENT'S CONDITION
 - 1 Preoperative severity is greater if
 - a Patient is cachectic
 - b Clinical myxedema is present
 - c Tumor is extensive
 - d Intracranial pressure is increased
 - e Anemia is severe
 - f Water test is positive
 - g Basal metabolic rate is low
 - h 17 Ketosteroids are decreased
 - 2 Postoperative prognosis is worse with
 - a Extensive pituitary extirpation
 - b Intracranial complications as
 - (1) Localized hemorrhage
 - (2) Edema of brain
 - c Infection
 - (1) Intracranial
 - (2) Elsewhere
 - d Hyperthermia
 - e Acute adrenal insufficiency
 - f Potassium loss, when marked
 - g Elevation of (possible delayed alarm reaction)
 - (1) Nonprotein nitrogen
 - (2) Sodium
 - (3) Chlorides
- B PREOPERATIVE CARE WHEN HYPOPITUITARISM IS PRESENT
 - 1 Desoxycorticosterone
 - a Indication—for severe adrenal insufficiency if ACTH or cortisone used not needed
 - b Dosage—parenteral 5 mg daily, 3 to 4 days before operation
 - 2 Adrenocorticotrophic hormone or cortisone
 - a Indication—when moderate or severe hypofunction exists—given 3 to 4 days before and after operation
 - b Dosage
 - (1) Cortisone—25 to 50 mg/day
 - (2) ACTH—40 mg/day or effective dose see 106 III E
 - 3 Testosterone propionate
 - a Indication—marked malnutrition

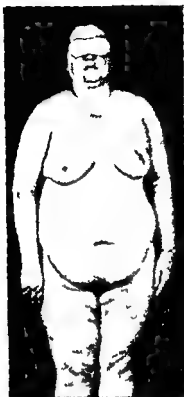


FIG 103 HYPOPITUITARISM—MIXED TUMOR (verified) Age 32 Chief complaints Failing vision 6 months amenorrhea and gain of 100 lbs in years Findings Skin smooth and pale Normal hair distribution Bilateral hemianopsia Plasma cholesterol 219 mg % BMR minus 30% FSH negative (twice) Sella enlarged with erosion into sphenoid sinus on left Microscopic diagnosis first operation predominantly chromophil growth Recurrence 18 months later unchanged by roentgen therapy Reoperation chromophobe tumor No restoration of vision



FIG 104 ANEURYSM OF RIGHT INTERNAL CAROTID Age 54 female Right optic atrophy was caused by this aneurysm Verified by operation The above roentgenogram was taken several years later after a thorotrast injection of the right common carotid artery Sella was not enlarged



FIG 105 PANHYPOTUITARISM—MIXED PITUITARY ADENOMA (verified) (Postoperative photograph) Age 26 Failing vision bitemporal headache loss of libido no beard Regression of secondary sex characteristics Note smooth feminine facial features Plasma cholesterol 116 to 136 mg % BMR minus 18% Craniotomy with restoration of vision and return of normal hormonal secretions

- d Tumor alterations
 - (1) Two common changes are
 - (a) Edema
 - (b) Hemorrhage
 - (2) Temporary increased pressure on optic nerves may occur from these two complications
 - (3) Check by frequent visual field examinations
- 3 Delayed
 - Develop after repeated series of roentgen radiation as much as 3 000 to 4,000 r to each skin area
- b The following may occur
 - (1) Atrophy of the
 - (a) Muscles
 - (b) Subcutaneous tissue
 - (c) Skin (with telangiectasia)
 - (d) Bones
 - (2) Brain fibrosis
 - (3) Depilation permanently

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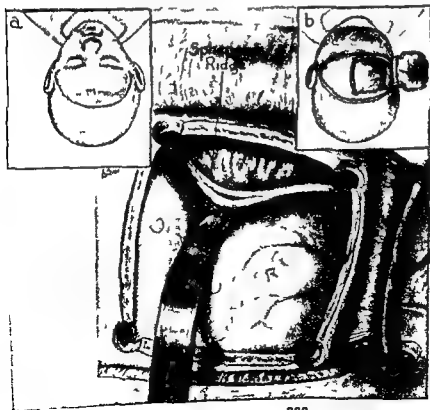


FIG 108 SURGICAL TREATMENT OF PITUITARY TUMORS Steps in the removal of a pituitary adenoma The large upper sketch shows the frontal lobe retracted after dura has been incised right optic nerve exposed and adenoma protruding medial to nerve (A) shows beginning removal of adenoma by scoop after incision into capsule Insert (B) illustrates wider opening of capsule and further evacuation of contents by suction Insert (C) shows removal of upper portion of capsule after it has been with drawn from under the optic nerves and chiasm (Horrax G The Pituitary Gland Baltimore Williams & Wilkins pp 665 682)

FIG 106 SKULL IN MIXED PITUITARY TUMOR
 Age 23 female Excessive perspiration enlargement of hands and feet also coarsening of facies Headache amenorrhea and blurred vision with bitemporal hemianopsia Hair normal No anemia BMR plus 15% Operation because of sudden increase in visual disturbance No preoperative roentgen therapy given Pathologic report adenoma of mixed chromophobe and eosinophilic type Note large sella and comparatively little bony change in skull



FIG 107 SURGICAL TREATMENT OF PITUITARY TUMORS Transfrontal craniotomy illustrating coronal incision entirely within hair line (a) Forward reflection of skin bone flap turned down over right frontal area (b) Retraction of dura over right frontal lobe and line of incision in dura along sphenoidal ridge (Horrax G The Pituitary Gland Baltimore Williams & Wilkins pp 665 682)



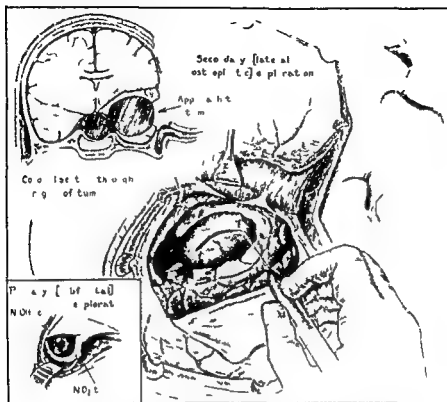


FIG 110 SURGICAL TREATMENT OF PITUITARY TUMORS Method of removing a large temporal extension of pituitary adenoma by a secondary (temporal) bone flap (Cushing H Intracranial Tumors Thomas Springfield Ill ■ 17)

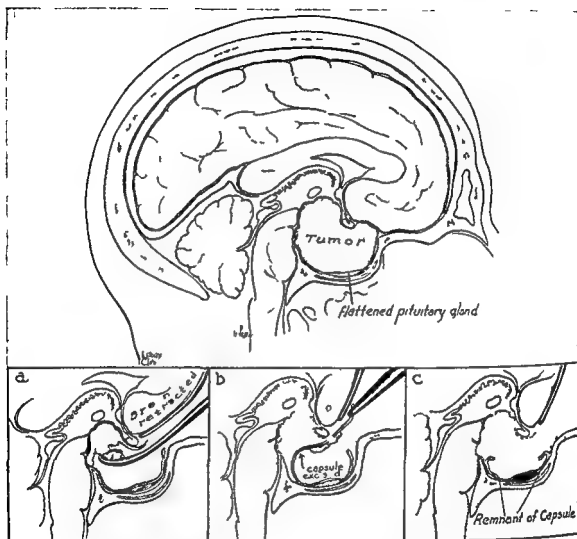


FIG 109 SURGICAL TREATMENT OF PITUITARY TUMORS Removal of large adenomas which have extended backward and upward behind the chiasm. Large upper diagrammatic sketch shows the relative size and situation of the tumor extending upward into the third ventricle and backward to compress the pons. Inserts (a), (b) and (c) illustrate the successive steps in removing the tumor contents, withdrawal and partial excision of capsule (Horrax G. *The Pituitary Gland* Baltimore: Williams & Wilkins pp 665-682).

CHAPTER 3

Thyroid

PRECLINICAL

Section 14 PRELIMINARY

- I HISTORY
- II ANATOMY
- III EMBRYOLOGY
- IV CONGENITAL ANOMALIES
- V HISTOLOGY
- VI FUNCTIONS
- VII CHEMISTRY
- VIII BIO ASSAY
- IX PATHOLOGY
- X CLASSIFICATIONS
- XI and XII CHIEF CLINICAL FINDINGS OF HYPOSECRETION
AND HYPERSECRETION
- XIII EXAMINATION OF PATIENT

CLINICAL

Section

- 15 ENDEMIC GOITER
 - 16 COLLOID GOITER
 - 17 NODULAR (MULTIPLE) GOITER
 - 18 INTRATHORACIC GOITER
 - 19 THYROIDITIS—ACUTE NONSUPPURATIVE AND
SUPPURATIVE
 - 20 CHRONIC NONSPECIFIC THYROIDITIS
 - 21 REIDEL'S STRUMA
 - 22 HASHIMOTO'S STRUMA
 - 23 INFECTIOUS GRANULOMATA
 - 24 CRETINISM
 - 25 MYXEDEMA
 - 26 HYPERTHYROIDISM
 - 27 PERSISTENT HYPERTHYROIDISM
 - 28 RECURRENT HYPERTHYROIDISM
 - 29 APATHETIC HYPERTHYROIDISM
 - 30 THE THYROCARDIAC PATIENT
 - 31 HYPERTHYROIDISM AND DIABETES MELLITUS
 - 32 HYPERTHYROIDISM AND PREGNANCY
 - 33 EXOPHTHALMIC SYNDROME
 - 34 FACTITIOUS HYPERTHYROIDISM
 - 35 TUMORS
-

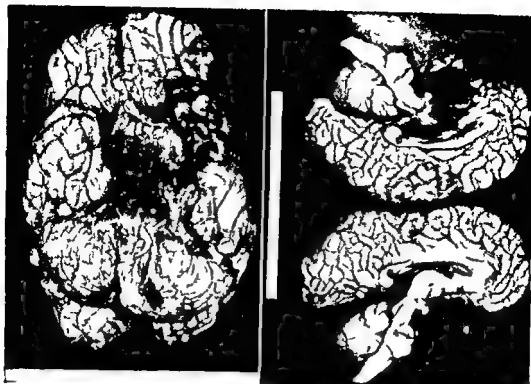


FIG 111 PITUITARY ADENOMA WITH LEFT TEMPORAL EXTENSION Patient was operated upon by Dr Harvey Cushing in 1930 for a large pituitary adenoma with an extension into left temporal lobe He remained well for approximately 8 years *Chief complaints* Decreased vision anosmia weakness of right side of body aphasia and mental deficiency lethargy and somnolence *Examination* Marked hypopituitary signs bilateral primary optic atrophy right lower facial weakness and overactive deep reflexes on right Blood count and urine normal Blood sugar 70 mg % Plasma cholesterol 2.5 mg % BMR minus 34% Patient had second operation in 1938 left temporoparietal craniotomy with extensive capsular and intra capsular removal of huge recurrent pituitary adenoma



FIG 112 PITUITARY ACIDOPHILIC ADENOMA A very large symptomless extension of a pituitary acidophilic adenoma into the right temporal lobe Homonymous hemianopsia was not found in spite of the size of the metastatic lesion (Cushing H and Davidoff L M The Pathological Findings in Four Autopsied Cases of Acromegaly with a Discussion of Their Significance Monograph Rockefeller Institute for Medical Research No 22 p 73)

PRELIMINARY SECTION 14

I HISTORY

About 700 B C

A.D. 23 79 Plinius¹¹¹

A.D. 130 200 Galen⁴
600

c. 630 Iulus Aegineta¹¹¹

1170 Roger of Salerno¹

1543 Vesalius¹⁴¹

1562 Reylidus Columbus³

1563 Gallopio³⁹

Early part
seventeenth
century

Paracelsus¹⁰⁰

1629 May¹⁰⁴

1656 Wharton¹⁰

1657 Hofer⁰⁷

1722 de Saint Yves³⁻

1749 Haller²⁰

1769 Prosser¹¹⁶

1786 Larry¹¹⁹

1800 Iodéré⁴⁹

1800 Hedenus⁶

1800 Piusuti¹¹³

1802 Flajani³⁰

1806 Meckel⁶⁸

1811 Burns¹⁷

1813 Blizard¹⁴

1813 Courtois⁷

1820 Coindet⁻

1830 Langl⁸

1832 Cooper¹

1834 Prout¹²⁷

1835 Graves⁴⁵

1835 N. R. Smith¹³³

Assyrian bas reliefs probably showed a case of exophthalmic goiter, medical scripts from ancient Egypt and Rome recognized the occurrence of goiter as due to some factor in water ingested; operative treatment mentioned, sculptures showed signs of goiter and exophthalmos.

Impure water said to be the cause of goiter.

Thyroid produces a lubricating fluid for the larynx.

Chinese treated cretinism with sheep thyroid glands.

Resection of goiter attempted.

Seaweed and sponges were used for treatment of goiter; surgery performed if these failed.

Thyroid gland described for the first time.

Thyroid gland weight stated to be a little over one ounce larger at birth and in females.

Congenital goiter recorded.

Relationship between cretinism and endemic goiter established.

Ligation of afferent arteries to thyroid.

Thyroid gland given its name.

Goiter may be produced by air, water and food.

Three patients with exophthalmos and goiter were reported.

Intrathoracic goiter noted.

First recorded use of an iodine preparation for the cure of goiter in England.

Classical account of exophthalmic goiter.

Cretinism considered to be due to concentrated air in deep valleys rather than to water, skeletal changes recognized.

Six successful operations for goiter.

Thyroid juice suggested as a therapeutic measure.

Exophthalmic goiter described and related cardiac disturbances noted.

Puberty and pregnancy cause an increase in size of the thyroid gland.

Carcinoma of thyroid reported.

Ligation of superior thyroid artery in treatment of toxic goiter.

Iodine obtained from seaweed.

Iodine used in treatment of thyroid disorders.

Intrathoracic goiter recognized clinically.

Enlarged thymus noted at postmortem in a case of Graves's disease.

Reports published on giving iodine compound in treatment of goiter (actually first used as a remedy for goiter in 1816).

Exophthalmic goiter described.

First operation for goiter in America.

1890	Lannelongue ⁸⁵	Thyroid transplantation for treatment of cretinism
1890	Vassale ¹⁵⁹	Thyroid extracts given to experimental thyroidectomized animals with improvement
1891	Murray ¹⁰⁹	A glycerin extract of a sheep's thyroid was injected hypodermically for treatment of myxedema with satisfactory results
1892	Mackenzie ⁸⁷ and Fox ⁴¹ (independently)	Myxedema treated with success by oral administration of dried thyroid gland
1893	Bruns ¹⁷	Caseous tuberculosis may develop in thyroid gland
1893	Greenfield ¹⁶	Thyroid hyperplasia caused increased functional activity in Graves's disease
1893	Joffroy ⁷⁷	Special eye sign reported in hyperthyroidism
1893	Müller ¹⁰¹	Increased basal rate and altered protein metabolism were discovered in exophthalmic goiter cases
1894	Beclère ¹⁰	Induced hyperthyroidism recognized
1895	Ballet and Enriquez ¹	Serum of myxedematous patients tried in treatment of toxic goiter
1895	Baumann ⁹	Thyroid contains iodine an iodine-containing compound (thyroiodin) isolated
1895	Magnus Levy ²⁰	Work of Müller confirmed and the foundation laid for the concept of thyroid function
1895	von Mikulicz ¹⁴⁷	First operation for relapse of exophthalmic goiter
1896	Riedel ¹²⁰	Chronic inflammation of thyroid described
1896	Vassale and Generali ¹¹⁰	Myxedema produced by thyroidectomy and removal of parathyroids caused tetania thyreopriva
1897	Brissaud ¹⁶	Thyroid infantilism demonstrated
1899	Oswald ¹⁰⁸	Thyroglobulin isolated from thyroid gland
1899	Schiff ¹⁷⁰	Substernal goiter illustrated by roentgenograms
1902	Pineles ¹²	Endemic (familial) cretinism with goiter observed
1903	Williams ¹	Roentgen therapy for toxic goiter
1904	MacCallum and Cornell ¹⁰⁶	Cervical sympathetic stimulation resulted in exophthalmos
1905	Abbe ¹	Radium inserted into thyroid for treatment of Graves's disease
1905	von Hansemann ¹⁰⁶	Enlarged thymus was cause of Graves's disease
1905	Hunt ⁷⁰	Acetonitril test showed that activity of thyroid preparations are proportional to their iodine content
1906	Gifford ⁴³	Special eye sign in exophthalmic goiter
1906	Schrager ¹²⁰	The term 'lateral aberrant thyroid' suggested
1907	Kocher ⁷³	First to stress treatment with iodine in exophthalmic goiter also advised removal of one lobe and isthmus with ligature of one thyroid artery on opposite side
1907	Ungermann ¹⁰⁹	Lingual thyroid discovered
1908	Hunt and Seidell ⁷¹	Pertinency of iodine to physiologic activity of thyroid preparations was proven
1908	Kocher ⁷³	Lymphocytosis in toxic goiter recognized
1908	Marine and Williams ⁶	Relationship of iodine to structure of thyroid gland was studied
1909	Dunhill ⁵⁴	Two stage operation for toxic goiter
1912	Hashimoto ⁶¹	Struma lymphomatosa described
1913	Mori ¹⁰⁰	Primary carcinoma of thyroid can cause hyperthyroidism
1914	Gudernatsch ⁴⁹	Thyroid feeding markedly increased metamorphosis in tadpoles but retarded somatic growth

1836	Cooper	Thyroidectomy in animals produced peculiar symptoms
1836	King ⁷	Endocrine function of thyroid gland suggested
1840	von Bräsdow ¹⁴²	Exophthalmic goiter discussed, iodine given to two patients with excellent results, exophthalmos due to increased connective tissue
1849	Begbie ¹¹	Exophthalmos was caused by increased vitreous humor
1849	Dalrymple ³⁰	Special eye sign demonstrated in exophthalmic goiter
1850	Curling ⁷⁹	Clinical picture of cretinism noted, and thyroid deficiency suggested as the reason
1851	Niépce ¹⁰⁰	Pituitary enlargement in cretins
1853	Demarres ³¹	Exophthalmos was the result of excessive fat in ocular tissues
1858	von Müller ¹⁴⁸	Spasm of smooth muscle fibers caused exophthalmos
1859	Schiff ¹⁷⁷	Fatal results of thyroidectomy preventable by intra abdominal transplantation of the gland
1863	Trousseau ¹³⁶	Effective trial of iodine in treatment of Graves's disease occurred by error
1864	von Graefe ¹⁴⁴	Diagnostic eye sign of exophthalmic goiter described
1867	Sick ¹³¹	First total extirpation of the thyroid in a child with a description of postoperative myxedema
1869	Cheadle ¹⁰	Transitory and favorable effect from iodine administration in exophthalmic goiter
1869	Stellwag ¹²⁵	Special eye sign noted in hyperthyroidism
1871	Fagge ³⁷	Cretinism due to absence or atrophy of the thyroid
1874	Gull ⁴⁹	Cause of myxedema established
1874	Watson ¹⁴⁹	Partial thyroidectomies performed for treatment of toxic goiter
1876	Runge, ¹ Cohnheim ¹	Metastatic thyroid growths without obvious carcinoma in that gland were observed
1877	Baber ⁷	Extensive histologic studies on the thyroid gland of many animals
1878	Kocher ⁷⁶	Thyroidectomies for hyperthyroidism performed more successfully
1878	Ord ¹⁰⁷	The term 'myxedema' was coined
1882	Reverdin ¹¹⁹	Myxedema produced in humans by partial or total removal of thyroid
1883	Kocher ⁷⁷	Myxedema following thyroidectomy was termed 'cachexia strumpriva'
1883	Marie ⁸⁰	Tremor was recognized as a sign of exophthalmic goiter
1883	Mobius ⁹⁹	Special eye sign demonstrated in hyperthyroidism
1883	Wolfier ¹³³	Classification of thyroid tumors
1884	Horsley ⁶⁸	Total removal of thyroid in a monkey induced myxedema (parathyroids were also extirpated)
1884	Rehn ¹¹⁸	Excess thyroid secretion caused Graves's disease
1885	His ⁶⁶	Double origin of human thyroid noted in embryos
1887	Savilli ¹⁻⁵	Myxedema common to both sexes
1888	Bernays ¹	Sublingual thyroid described
1888	Rogowitsch ¹⁻³	Thyroidectomy in rabbits resulted in pituitary hypertrophy
1890	Bettencourt and Serrano ¹³	Thyroid grafts produced temporary relief of myxedema

1932	Marine Spence and Cipra ⁹¹	Injections of methylecyanide caused chronic bilateral exophthalmos in rabbits
1932	Naffziger and Jones ¹⁰	Fibrosis and lymphocytic infiltration of degenerated muscles resulted in exophthalmos bilateral orbital decompression advised
1933	Blumgart, Levine and Berlin ¹	Angina pectoris and congestive heart failure treated by thyroidectomy
1933	Marine and Rosen ⁹³	Anterior pituitary extracts produced exophthalmos in thyroidectomized guinea pigs
1934	Drouet ⁹⁵	Graves's disease was due to hyperpituitarism (an excess of thyrotropic hormone) with resulting hyperthyroidism
1934	Ilmer and Scheps ⁹⁵	Blood iodine parallels basal metabolic rate
1934	Étienne and Drouet ⁹⁷	Deep roentgen therapy of pituitary for Graves's disease
1935	Zeckwer Drivison Keller and Livingood ¹	Stunting of growth in the cretin rat might be due to a decrease in acidophilic cells of the pituitary
1938	Hertz Roberts and Evans ⁴ Hamilton ¹	Radioactive iodine studied as an indicator of thyroid physiology
1939	Hamilton and Soley ⁹³	Iodine metabolism analyzed by radioactive isotope in different types of thyroid disease
1940	Hamilton Soley and Eichorn ¹	Radioactive iodine uptake in carcinoma of the thyroid was reported
1941	Mackenzie Mackenzie and McCollum ⁹⁶	Sulfaguanidine has goitrogenic effects
1941	White and Ciereszko ¹	Thyrotropic hormone purified
1942	Hamilton and Lawrence ¹ also Hertz and Roberts ⁹¹	Radioactive iodine therapy for hyperthyroidism
1942	Keston Balf Frantz and Palmer ⁷⁴	First positive evidence of pickup of radioactive iodine by a metastatic lesion from a carcinoma of the thyroid
1943	Astwood ⁹⁵	Thiouracil depressed the production of thyroid hormone and was effective in treatment of hyperthyroidism
1943	Griesbach and Purves ⁹⁷	Thyrotropic content of pituitary diminished in proportion to the decrease in acidophilic cells in thyroidectomized rats; serum thyrotropic hormone was increased
1947	Cope Rawson and McArthur ⁹	Hypersecretory solitary adenoma proved by radioactive iodine studies

II ANATOMY

A LOCATION

- 1 A bilobed encapsulated gland
 - a Lying on either side of the trachea
 - b Extending from the second to the fourth tracheal cartilage and occasionally to the first
- 2 Muscles covering it
 - a Sternocleidomastoid
 - b Sternohyoid
 - c Sternothyroid
 - d Omohyoid

B DESCRIPTION

- 1 Color
 - a Reddish
 - b Grayish brown
- 2 Consistency—slightly firm
- 3 Shape
 - a Smooth
 - b Irregular
 - c Anteriorly—convex
 - d Posteriorly—concave
- 4 Capsule sends thin fibrous septa into the stroma to form irregular incomplete lobulations

1914	von Haberer, ¹⁴⁵ Halsted ¹	Thymectomy for toxic goiter
1914	Hertoghe ⁶³	Anginal pain noted in myxedematous patients
1914	McCarrison ⁹⁷	Pathogenesis of experimentally produced goiter reported
1915	Cannon, Binger and Fitz ¹⁸	Symptom complex of Graves's disease developed in a cat after suture of superior cervical sympathetic to phrenic nerve
1915	Halsted	Roentgen therapy over thymus for Graves's disease
1915	Kendall ⁷³	Crystalline thyroxin isolated
1916	Smith ¹³³	Hypophysectomy produces thyroid atrophy
1917	Marine and Kimball ⁹⁹	Iodine used for prevention of simple goiter
1918	Allen, ³ Hoskins and Hoskins ¹ (independently)	Metamorphosis and development of skeleton prevented in tadpoles by thyroidectomy
1918	Luden ⁶	Blood cholesterol is elevated in myxedema
1918	Zondek ¹³⁵	Description of "myxedema heart"
1919	Goetsch ⁴⁴	Epinephrine sensitiveness in hyperthyroidism suggested as a diagnostic aid
1920	Loeb ⁹³	Thyroid tissue may respond with increased activity to a deficit or excess of iodine
1921	Shapiro and Marine ¹³⁰	Adrenal cortices from oven benefited patients with toxic goiter
1922	Marine and Baumann ⁹¹	Adrenalectomy or freezing adrenal cortices in rabbits produced clinical picture of Graves's disease
1922	Murray ¹⁰⁰	Exophthalmos due to edema of tissues
1922	Smith and Smith ¹³⁴	Pituitary elaborates a hormone which stimulates the thyroid
1923	Plummer and Boothby ¹¹	Iodine used for preoperative treatment of exophthalmic goiter
1924	Lahey and Hamilton ⁸⁰	The term "thyrocardiac" coined
1925	Craver ²⁶	Irradiation of thyroid for carcinoma
1926	Harington ⁷	Thyroxin is a derivative of tyrosine
1926	Uhlenhuth and Schwartzbach ¹³⁷	Acid extracts of pituitary stimulated the thyroids of salamanders
1927	Harington and Barger ⁸	Synthetic thyroxin discovered
1928	Chesney, Clawson and Webster ²⁰	Cabbage has goitrogenic properties
1928	Rienhoff and Lewis ¹³⁶	Thyroid histologic changes during remission of hyperthyroid patient described
1929	Harington and Randall ⁹	Diiodotyrosin isolated from thyroglobulin
1930	Aron ⁴	Urine of toxic goiter patients contains less thyroid stimulating principle than normal
1930	Harington and Salter ⁶⁰	Thyroid hormone stored in gland as colloid
1930	Mason, Hunt and Hurxthal ⁹³	Blood cholesterol shown to fluctuate with thyroid function
1931	Abelin	Diiodotyrosin prepared
1931	Loeb and Friedman ⁸⁴	Chronic treatment with anterior pituitary thyrotropic extract resulted in a state of refractoriness to the effects of the injected substance
1931	Schockaert ¹⁸	Exophthalmos demonstrated in ducks following thyrotropic hormone injections
1932	Aron and Benoit	Serum and urinary thyrotropic hormone are increased in thyroidectomized animals

G NERVES^{6 7 8}

- 1 Fibers follow arteries and end in dense networks surrounding each follicle
- 2 Nonmyelinated postganglionic fibers from middle and inferior cervical ganglia of sympathetic system
- 3 Parasympathetic fibers may come from
 - a Vagus
 - b Laryngeals
 - (1) Inferior
 - (2) Superior
 - (3) Recurrent (see Chart 27)
 - c Ansa hypoglossi
 - d Carotid plexus

III EMBRYOLOGY (development in weeks)^{2 5}

- A THREE (14 mm) — Entodermal lining thickens medially into an evagination between the first and the second pharyngeal pouches
- B FIVE (55 mm)
 - 1 Bilobed sac with stalk develops
 - 2 Stalk (neck) a narrow tube is known as thyroglossal duct
- C SIX (11 mm)
 - 1 Solid epithelial plates form
 - 2 Exaginations from the fourth entodermal pouch give rise to the lateral thyroid components (questionable)
 - These grow forward and upward to meet the posterior surface of the median lobe
 - The three portions begin to fuse into one
 - 3 Thyroglossal duct
 - a Development—separates from pharynx and atrophies
 - b Point of origin on tongue remains permanently known as the foramen caecum
- D SEVEN (17 mm) — Single lobe lies on either side of trachea
- E EIGHT (25 mm)
 - 1 Follicle formation begins⁷
 - 2 Ingrowth of
 - a Connective tissue
 - b Blood vessels
- F ELEVEN TO FOURTEEN (60 to 100 mm)
 - 1 Secretory follicles appear^{1 6}
 - 2 Colloid develops^{7 11}
 - 3 Thyroxin is found⁸

- 4 Total iodine present in fetal thyroid glands varies from 1 to 19 micrograms from third to ninth month⁹
- 5 Radioactive iodine is collected by the thyroid¹

G TWENTY (160 mm) — Maximum number of follicles, thereafter growth in size only

IV CONGENITAL ANOMALIES

- A ABSENT (see 24) ^{4 6 11 1 14}
- B APLASIA (see 24) ^{4 6 11 1* 14}
- C PYRAMIDAL LOBE (one third to one half of cases normally)^{9 1}
- D LINGUAL THYROID (see 35 VII H)^{10 13 17}
- E ABERRANT TISSUE^{2 9}
 - 1 Intrathoracic (see 18)
 - 2 Lateral (see 35 VII B)^{7 10 13}
- F TERATOMAS (containing thyroid tissue)
 - 1 Ovaries (see 78 IV) ^{8 1 10 10}
 - 2 Branchial clefts
- G THYROCLOSSAL DUCT (see 35 VII C) — Gives rise to
 - 1 Accessory thyroid glands
 - 2 Fistulae
 - 3 Cysts^{1 7}

V HISTOLOGY ^{2 13}

- A FOLLICLES (acini) (see Fig 114)
 - 1 Basic units
 - 2 Variations in
 - a Shape
 - (1) Ovoid
 - (2) Spherical
 - b Size—50 to 300 microns
 - c Number
 - 3 Lumina may be
 - a Small
 - b Large
 - 4 Lining of a single cellular layer resting on a very delicate reticular connective tissue (no basement membrane)
- B INTRAFOLLICULAR COLLOID (see 14 VI E 2 c)
 - 1 Amount present is variable depending on degree of thyroid activity
 - 2 Acidophilic stain taken by colloid which is more pronounced in center of follicle especially when epithelial cells are active
 - 3 Vacuolated appearance — scalloped edges with active transfer of colloid from follicle to cell or vice versa

- 5 Thymus and parathyroids may be within it
- 6 Accessory tissue may be present in
 - a Base of tongue (lingual thyroid)
 - b Neck
 - Thyroglossal duct
 - d Thymus
 - e Mediastinum
 - f Struma ovarii

C PARTS (see Fig 113)

- 1 Isthmus
 - Connects the two lateral lobes of the thyroid (an H shape or butterfly)
- b May be
 - (1) Absent
 - (2) Separate from both lobes
 - (3) Varied in size, $\frac{1}{2}$ in breadth and depth usually
- 2 Pyramidal process, a cordlike structure, arises from the isthmus which may
 - a Lie to left of midline in front of cricoid and thyroid cartilages
 - b Extend toward and up to hyoid bone
 - c Be
 - (1) Absent
 - (2) Double
 - (3) Separate from lateral lobes
 - (4) Any size

D WEIGHT

- | | Gm | |
|--|---|--|
| 1 Newborn | 15 25 (0.06% of body weight) ³ | |
| 2 Tenth year | 10 ³ | |
| 3 Puberty | 15 ³ | |
| 4 Adult | | |
| a Range | 8 60 2 4 9 | |
| b Average | 20 28 (0.4 Gm/Kg of body weight) ^{1 2} | |
| 5 Right lobe ■ slightly larger than left | | |
| 6 Normal increase in size and weight at | | |
| a Puberty | | |
| b Premenstrual phase | | |
| c Pregnancy | | |
| ■ Menopause | | |

E SIZE⁰

- | | CM |
|-------------|-------|
| 1 Length | 5 8 |
| 2 Width | 2 4 |
| 3 Thickness | 1 2 5 |

F BLOOD AND LYMPH SUPPLY

- 1 Arteries

- a Superior thyroids (one from each side) from external carotids
- b Inferior thyroids (one from each side) from subclavian vessels ■ thyrocervical trunk
- Thyroid ima (fifth artery not constant) from arch of aorta or innominate
- d Aberrant arteries (collaterals) may originate from
 - (1) Tracheal
 - (2) Pharyngeal
 - (3) Esophageal
- Vessels anastomose on the surface of gland
 - (1) Blood supply is abundant¹
 - (a) 3 5 6 cc/Gm of tissue/min (or 5 liters/hr for whole gland)
 - (b) Many anastomoses
 - (c) Blood vessels are large
 - (2) Capillary network encircles each follicle

2 Veins

- a Commence as a perfollicular plexus
- b Follow small arteries
- c Empty as
 - (1) Superior thyroid (two usually) into internal jugular or common facial
 - (2) Inferior thyroid (two most frequently) into innominate or internal jugular
 - (3) Middle thyroid (not constant) into internal jugular
 - (4) Branch from pyramidal lobe in to one of anterior jugulars
 - (5) Thyroidea ima (one or two occasionally) into left innominate or venous angle

3 Lymphatic vessels

- a Form a rich plexus surrounding each follicle
- b Correspond to blood vessels
- Drain into nodes of
 - (1) Deep cervical region
 - (2) Lateral and front portions of trachea
 - (3) Supraclavicular area
 - (4) Prelaryngeal
 - (5) Upper mediastinal (occasionally)
- d May empty directly into subclavian vein

- f Intracellular colloid
 - (1) Appears as droplets in apical portion of columnar cell
 - (2) Is rare in cuboidal cells

D CONNECTIVE TISSUE

- 1 Forms capsule which surrounds entire gland
- 2 Sends prolongations between the follicles (intrafollicular stroma) composed of
 - a Collagen
 - b Elastic fibers
- 3 Contains abundant
 - a Blood vessels
 - b Lymphatics
 - c Nerves

VI FUNCTIONS

A GLAND AS A WHOLE (see Chart 48 p 478)

- 1 Thyroid gland secretes and elaborates ingredients for the synthesis of thyroid hormone (which as yet has not been identified)
- 2 Thyroid hormone provides the necessary chemical and physiochemical stimuli to cellular processes which in total maintain the normal reaction and character of existence
- 3 Although nonessential to life it is indispensable for normal growth and development
- 4 Thyroid hormone inhibits the production of pituitary thyrotropic hormone (TSH)

B THYROID HORMONE (studied by giving thyroxin or desiccated thyroid similar effects are produced by thyrotropic hormone—see 2 VI B 5 14 VI C D)

- 1 Stimulation of
 - a All oxidative processes by effect on
 - (1) Permeability of cellular membrane
 - (2) Physiologic action on the cell surface
 - (3) Oxygen supply to tissues
 - b Normal somatic growth and development^{13 14 16 19 23 3 38}
 - c Nervous irritability
 - d Cardiac rate and output^{23 38 44 4}
 - e Blood volume^{1 34}
 - f Specific dynamic action of food stuffs

2 Metabolic influence

a Carbohydrate

- (1) Decrease in
 - (a) Liver and muscle glycogen^{1 27 27 30}
 - (b) Glucose and galactose tolerance
- (2) Increased¹¹
 - (a) Glycogenolysis
 - (b) Blood sugar (slight)
 - (c) Intestinal absorption *

b Fat

- (1) Direct action may be on fatty tissue
- (2) Indirect action is more likely by increased
 - (a) Expenditure of energy
 - (b) Muscular activity
- (3) Decreased blood^{20 1}
 - (a) Cholesterol
 - (b) Lipase¹

c Protein^{10 34}

- (1) Exogenous and endogenous breakdown—increased
- (2) Urinary excretion—increased¹⁸
 - (a) Nitrogen (no change in rats)
 - (b) Urea
 - (c) Creatine
- (3) Blood urea—decreased
- (4) Muscle creatinine (cardiac and skeletal)—decreased^{1 6 7 8 9 30 37}

d Water elimination is increased through¹

- (1) Kidneys
- (2) Bowels

e Miscellaneous

- (1) Urinary excretion—increased in
 - (a) Calcium, probably direct stimulation rather than through the parathyroids
 - (b) Phosphorus
 - (c) Iodine
- (2) Phosphatase content increased in
 - (a) Diaphyses
 - (b) Epiphyses
- (3) Blood iodine (organic or protein bound)—increased

C THYROIDECTOMY (Composite survey of human and animal observations—see also 14 VI VII)

- 1 Greatest changes in younger animal

C CELLULAR STRUCTURE (epithelium)

1 Types of cells

a Epithelial or 'chief'

(1) Resting stage

(a) Shape

- [1] Cuboidal when cut perpendicular to base
- [2] Polygonal tetrahedron or circular appearance when sectioned parallel with base

(b) Size (average)

- [1] Base diameter—15 microns
- [2] Height when cuboidal—15 microns

(c) Nucleus

- [1] Large
- [2] Spherical
- [3] At base

(d) Colloid—rarely found

(e) Chromatin—poor

(f) Basement membrane—absent

(g) Function—secretory function slight, may be inactive (resting)

(2) Hyperactive stage

(a) Shape—columnar

(b) Size—height greater than 15 microns

(c) Nucleus—same as in cuboidal cell

(d) Colloid content—increases (globules)

(e) Other cellular elements—increase (see below)

(f) Function—few of these are present in normal resting gland

(3) Nonfunctioning stage

(a) Shape—flat

(b) Nucleus—pyknotic

(c) Cytoplasm—stains like colloid in some

(d) Cellular elements—decrease

(e) Function—probably none

b Parafollicular (interstitial or intervesicular)¹¹

(1) Location in interalveolar spaces

(2) Belief is that they may be

- (a) Embryonic cells which form new follicles

(b) Resting stage of glandular tissue

(3) Functions—possibly

(a) Absorption

(b) Secretory

(c) Formation of new acini

2 Cellular components

a Mitochondria¹¹

(1) Types

(a) Granules

(b) Filaments

(c) Rods

(2) Size and number increased with hyperactivity^{1, 10}

(3) Functions

(a) Intracellular surface may be increased by mitochondria, for lipoids can concentrate upon them

(b) If mitochondria disappear the lipoids return to the cytoplasm (decreased activity)

(c) Above changes may affect cellular permeability

b Golgi apparatus^{1, 10, 11, 17}

(1) Reticular structure

(2) Position may indicate the direction of cellular secretion, if at¹³

(a) Apex—hypersecretion

(b) Base—hyposecretion

(3) Hypertrophy of the apparatus indicates increased activity

(4) Colloid droplets develop near by with hypersecretion

c Oxidase granules are^{1, 16}

(1) Increased in size and number with cellular hyperactivity, opposite with hypofunction

(2) Seen in colloid with hyperactivity

(3) Indices of enzymic oxidation activity

d Alkaline phosphatase^{5, 7}

(1) Varies, but in an unknown manner

(2) Decreases after hypophysectomy

■ Vacuoles

(1) Increase with cellular hyperactivity and vice versa

(2) Are considered to be artifacts by de Robertis (see Fig 117)⁵

- (4) Thyrotropic hormone in¹
 - (a) Urine—absent
 - (b) Serum—decreased
- (5) Growth hormone increased (?)
(see 23 VI B)
- (6) Diabetes insipidus (see Protocol 8 \IV)²³
 - (a) Animals—variable reports
 - (b) Humans—diuresis increased

b Parathyroids—data inconclusive

c Adrenals

- (1) Cortical size—increased usually
4 5, 7 8 10 11 14 16 20 26
- (2) Epinephrine sensitivity — increased^{7 14}
- (3) 17 ketosteroid excretion — decreased

d Gonads

- (1) Function—decreased^{1 11 15 19 21 23}
- (2) Weight—variable seminal vesicles decreased^{1 7 20}
- (3) Sperm—decreased or no change¹
- (4) Ovulation—decreased (?)

e Pancreas

- (1) Weight—increased^{10 7 23}
- (2) Diabetes mellitus—made worse

f Thymus—size variable may persist
3 7 9 1

E HISTOPHYSIOLOGY (see Figs 115 117)

1 Origin of secretion

a Thyroid hormone or its precursor is manufactured and stored within the thyroid gland

b Extrathyroidal source or synthesis has been postulated (see 14 VI F 1 h)

c The level of thyroid activity is mediated directly by the thyrotropic hormone (TSH) of the pituitary (see 2 VI B 5)

d The gland has an independent (of pituitary) level of activity to

- (1) Utilize iodine
- (2) Form thyroid hormone

2 Concept of normal function

a Introduction

- (1) The concept that the thyroid gland secretes a hormone or its precursor to fulfill the body needs and stores the excess as colloid is generally accepted
- (2) Thyroid cells absorb inorganic iodide which is

(a) Synthesized into iodine compounds (organic protein bound)

(b) Stored in the follicles as colloid

{3} When a demand exists for more hormone, the colloid is

(a) Absorbed by the cells unless irrevocably trapped

(b) Converted presumably into hormone which is secreted into the blood stream

{4} The chemical form of the iodine bearing compound or compounds when secreted or circulating in the blood stream is unknown

{5} It is possible that the true hormone is born only when the iodine complexes escape into the circulating blood

{6} When the hormone supply is adequate the gland is pictured as storing colloid the cell polarity being central

{7} When a demand for hormone increase, the thyroid cells may be considered temporarily at a standstill until the reversal of polarity takes place, the direction of flow then is from the follicle through the cells into the blood stream or the lymphatics¹{8} It is not likely that this reversal of movement would affect every follicle in exactly the same degree at all times so that only a few would be called upon to supply a small increase in demand¹{9} Wahlberg we conclude believes that under normal conditions²⁰

(a) The vast majority of follicles are resting i.e. neither secreting into the blood stream or follicle

(b) Only a rare follicle supplies the needed hormone and is found in a secretory state

{10} Radioactive iodine experiments¹⁵

- 2 Retardation of all metabolic processes, except elaboration of thyrotropic hormone
- 3 Cessation of ^{7 80}
 - Growth
 - b Development
- 4 Premature senility
- 5 Mental deterioration
- 6 Weight gain
- 7 Trophic disturbances of
 - a Skin
 - b Hair
 - c Osseous system
- 8 Body temperature reduced
- 9 Cardiac and nervous functions are suppressed
- 10 Lactation may or may not be affected¹⁹
- 11 Abdominal distention
- 12 Musculature (see 103 V)
 - a Decreased content of
 - (1) Glycogen
 - (2) Fat
 - b Increased content of creatine in⁶⁴
 - (1) Cardiac
 - (2) Skeletal
 - c Hypotonicity
- 13 Reproductive system delayed^{20 1}
- 14 Liver glycogen increased⁶⁴
- 15 Intracellular edema increased, extracellular decreased
- 16 Protein stored in body fluids
- 17 Specific dynamic action of foods is lost
- 18 Urinary excretion—decreased
 - a Nitrogen
 - b Urea
 - c Creatine³⁴
 - d Calcium
 - e Phosphorus
 - f Iodine
 - g 17 ketosteroids
- 19 Blood chemical analyses
 - a Decreased
 - (1) Sugar (may be slight)⁷⁰
 - (2) Iodine
 - b Increased
 - (1) Urea
 - (2) Cholesterol¹⁷
 - (3) Lipase
- 20 Effect on other glands
 - a Pituitary
 - (1) Hypertrophy rarely atrophy in young ^{6 7 9 13 14 8 79 33}
^{3 36 37 4 41 46 48 1 5 3 60}
^{67 69 7 7 76 78 79}

(2) Histologic changes—see 2 IX
II 14³ 8 70 4 6 III 41 30 65
63 64 66 67 68 69 70 83 8

(3) Hormonal content
(a) TSH—decreased or increased^{7 4}
(b) FSH—variable^{1 8 10 16 46}
III 1 7 73 7 8

(4) Thyrotropic hormone in
(a) Urine—increased^{11 15 37 48}
(b) Serum—increased^{4 43}

(5) Growth hormone decreased
(6) Diabetes insipidus^{1 77}
(a) Animals—variable results
(b) Humans—improvement

b Parathyroids—data inconclusive
■ Adrenals
(1) Cortical size—variable^{4 III}
^{30 31}

(2) Epinephrine sensitivity—decreased⁴⁷

(3) 17 ketosteroid excretion—decreased

(4) ACTH response—decreased⁴

d Gonads
(1) Function—decreased^{10 19 38-41}
^{47 57 61 60 7 74}

(2) Weight^{61 III 72}
(a) No change
(b) Decreased (seminal vesicles especially)

(3) Sperm—decreased^{1 61 69}

(4) Ovulation—decreased¹⁰

■ Pancreas
(1) Diabetes mellitus improves¹
(2) No change in insulin sensitivity^{1 9}

f Thymus—size variable ^{38 43 III}

D HYPERHORMONAL EFFECTS (see 14 VI VII)

1 On various organs and functions are summarized under

- a Thyroid hormone
- b Hyperthyroidism
- c Factitious hyperthyroidism

2 On other endocrine glands

- a Pituitary
 - (1) Size—decreased may be enlarged^{4 7 15}
 - (2) Histologic changes—see 2 VII B
^{154 15 13 19}
 - (3) Hormonal content
 - (a) TSH—decreased¹⁷
 - (b) FSH—variable^{4 9 77}

- e A goiter may be produced in the fetus by
 (1) Gonitrogenic agents^{8 11 16 21 21 21 4}
 (2) Iodine lack^{20 20 31}
 f Congenital athyroids are born with a retarded bone age but are usually normal in size^{10 15}
 g The organic blood iodine of the umbilical cord is much lower than that of the mother suggesting that each has its own level of thyroid hormone^{1 19 1}

TABLE 10 BLOOD IODINE IN MOTHERS AND NEWBORNS*

Case	TOTAL (WHOLE) BLOOD IODINE MICROGRAMS %		ORGANIC (WHOLE) BLOOD IODINE MICROGRAMS %	
	Mother	Cord	Mother	Cord
1	00	55.0	65.7	29.6
2	33.8	35.0	26.7	30.0
3	72.8	41.3	36.9	12.2
4	60.0	22.8	41.5	9.6
5	22.8	68.2	19.4	8.5
Average	51.9	45.4	38.0	13.6

* We are indebted to Drs. Frederic C. Irving and E. A. Brubaker for procuring these blood samples.

h Myxedematous mothers may

- (1) Improve during pregnancy^{7 32 40 43} thus if thyroid hormone of fetus does not pass the placenta an extrathyroidal origin of hormone may be hypothesized possibly in the ovaries (see 100 I B 2)^{1 4 8 7 17 22 30 31 39}

(2) Give birth to

- (a) Cretins with or without goiters
 (b) Normal children

1 Hyperthyroidism and pregnancy—see 21

2 Thyroid activity occurs before cell differentiation takes place in pituitary⁷

3 Infancy and childhood—continuation of thyroid function from intra uterine life with gradual increase in hormone production to meet the needs for growth and development

4 Puberty—a spurt in thyroid activity is thought to occur for the physiologic

changes with development in sexual function and body demands

5 Adult—secretion of thyroid hormone is related to general physiologic requirements

a Premenstrual phase—thyroid may enlarge and show increased activity

b Pregnancy—thyroid function gradually increases to meet the extra demands

c Temporary increased function is mediated through hypothalamus and pituitary (section of pituitary stalk prevents this in animals), with subsequent return to normal in most individuals with

(1) Emotion

(2) Cold

(3) Shock

(4) Exercise

6 Climacteric—thyroid function increases for a while and then decreases to correspond with the slowing down of bodily function

7 Old age—further retardation of all processes is followed by a similar decrease in thyroid function

G ANTITHYROID DRUGS

1 Experimental administration of thiouracil in animals and humans

a Thyroid effects—see 14 I A B 1 d

b Pituitary—see 2 I A B 22 k

c Growth retardation²

d Adrenal cortices atrophy¹

e Liver⁴

(1) Weight—increased

(2) Fat and cholesterol—unchanged

(3) Glycogen—increased

f Fate^{6 15}

(1) Gastro intestinal absorption is rapid

(2) Distribution

(a) Tissues greatest in

[1] Thyroid

[2] Ovaries

[3] Pituitary

[4] Bone marrow

[5] Liver

(b) Body fluids

(3) Storage in thyroid is¹⁻

(a) Increased by TSH

(b) Decreased by potassium iodide

- (a) Young animals (guinea pigs, rats)—all follicles are at same stage of activity
 - (b) Older animals—follicles differ in stages of activity
 - b Mechanism of iodide absorption, breakdown and utilization by the thyroid gland ^{7 9 11 13 16}
 - (1) Absorption of iodide and tyrosine from the blood stream by the thyroid epithelium
 - (2) Breakdown within the cell of iodide to free iodine by peroxidase an oxidative enzyme^{6 8}
 - (3) Synthesis of diiodotyrosine, thyroxine and colloid as follows
 - (a) Formation of diiodotyrosine from free iodine and tyrosine (also from blood stream)^{1 12}
 - (b) Coupling of two molecules of diiodotyrosine to form thyroxine¹⁴
 - [1] This is possibly due to cytochrome oxidation system
 - [2] Manganese may act as a catalyst¹⁷
 - (c) Linkage of diiodotyrosine and thyroxine into large complex molecule as colloid
 - (d) Iodine may also be fixed in gland without diiodotyrosine and thyroxine formation
 - (e) Mobilization of colloid droplets at cellular apex (side facing follicle) is seen chiefly in hyperactivity
 - (f) Colloid molecule is too large for extrusion through cellular membrane^{3 4}
 - c Formation of follicular colloid
 - (1) Proteolytic enzyme of the thyroid cell breaks colloid droplets into smaller extrudable particles which are secreted into the follicle^{3 13 19}
 - (2) Intrafollicular colloid is largely thyroglobulin which must be formed by some intrafollicular system, the nature of which is unknown
 - (3) Iodine contained in the follicle is in the form of
 - (a) Diiodotyrosine—70 to 80 per cent
 - (b) Thyroxine—20 to 30 per cent
 - (4) Diiodotyrosine and thyroxine are linked together as thyroglobulin
 - (5) Ovidase granules appear in the intrafollicular colloid as if secreted from the cell and may be factors in thyroglobulin synthesis
 - (6) In abnormal states colloid
 - (a) May be
 - [1] Inactive (biologically i.e., hypothyroidism)¹⁴
 - [2] Stained poorly
 - (b) Is not strictly thyroglobulin, for it may lack
 - [1] Iodide
 - [2] Diiodotyrosine
 - [3] Thyroxine
 - d Resorption of colloid and secretion of hormone is regulated by a proteolytic enzyme which⁶
 - (1) Is secreted into the follicle
 - (2) Breaks down colloid into small particles that are
 - (a) Resorbed
 - (b) Passed to base of cell
 - (c) Secreted into capillaries
- F ACTIVITY AT DIFFERENT PERIODS IN LIFE
- 1 Intrauterine
 - a The placental role in the maternal fetal relationship is an important one in the production of
 - (1) Congenital goiter
 - (2) Cretinism
 - (3) Congenital athyreosis
 - b Placenta permits passage of
 - (1) Iodine ^{1 20 31}
 - (2) Goitrogenic agents^{8 14 16 17 31 34}
 - (3) Thyrotropic hormone probably^{9 34 41}
 - (4) Virus infections^{3 1 13 19 37}
 - c Passage of thyroid hormone through the placenta is unlikely for it is not found in
 - (1) Urine
 - (2) Milk
 - (3) Saliva
 - d Fetus may require little, if any thyroid hormone until the late stages of development^{6 10 11 24 25 8}

3 Preparations of unknown biologic activity

B GUDERNATCH TADPOLE TESTS⁴

1 Normal larvae can metamorphose within 18 hrs by feeding thyroid tissue rather than the usual 10 to 12 weeks

2 Thyroidectomized larvae

- a Do not metamorphose, but can grow larger in size
- b Given thyroid, they will develop at a normal rate

3 Inorganic iodine fed to thyroidectomized tadpoles produces same results¹¹

4 Axolotls may be used instead

5 Effect of thyroxin on growth of white rats and rabbits can be determined¹²

C ACETONITRIL TEST¹³

1 Mice (or guinea pigs) are fed thyroid equivalent to 7 per cent of food intake for 2 to 14 days (usually 7 days)

2 Acetonitril dissolved in water is injected subcutaneously

3 Fatal dose for controls is 32 mg/Gm of mouse

4 Minimal fatal dose of acetomitril is not less than 14 mg/Gm of mouse

5 Sensitivity of test—1 mg of desiccated thyroid mixed 40 000 times its weight of cracker diet can be detected

D OXYGEN CONSUMPTION TESTS

1 Oxygen consumption of rats (rabbit dog guinea pig with or without thyroid gland may be used)^{9 10}

a Special apparatus for study of gaseous metabolism of rats (or other animals) is required

b Definite criteria for the experiment are followed (i.e., room temperature diet, etc.)

c Adequate dose of thyroxin is injected subcutaneously or desiccated thyroid is given orally

d Oxygen consumption increases after 18 hrs with a maximum in 48 hrs

e The resting oxygen consumption at 25° 14.44 ± 0.07 cc/Kg/min or 700 calories/sq m/24 hrs

f Percentage increase is calculated by comparison of (a) and (e)

2 Oxygen consumption in athyreotic humans⁹

a Patients with definite untreated spontaneous myxedema are used in

which metabolism rate is constant (average minus 38%)

(1) Men between 20 to 50 years of age average 23.5 calories/sq m/hr

(2) Women of these ages average 22.0 calories/sq m/hr

b The preparation to be tested may be given

(1) Orally or intravenously

(2) Single massive or divided doses

c Daily rise in basal metabolic rate is observed

(1) Average slope (oral administration) is 2.5 points/24 hrs

(2) Single dose produces a peak on the fifth day

(3) Divided doses cause a maximum rise by the twelfth day

d Every subject when given identical amounts of hormone will show the same rate and rise in basal metabolic rate

e Calorigenic activity of whole thyroid is related to the amount of organic iodine, not the thyroxin iodine

f Test gives accurate results but is impractical for routine assay

E CHEMICAL ASSAY⁵

1 A suitable amount of material usually 25 tablets, each equivalent to 5 gr of fresh thyroid gland, are

a Ground and suspended in 10 parts of normal sodium hydroxide solution

b Boiled under reflux condenser for 4 hrs

2 Hot solution is filtered quantitatively from traces of inorganic material and an aliquot portion is analyzed for iodine

3 Total iodine content of original samples is calculated

4 Remainder of filtrate is adjusted to a pH of 5.0 by addition of 50 per cent sulfuric acid and left overnight

5 Second quantitative filtration is done

a Filtrate analyzed again for iodine

b Difference between first and second analyses gives value of the acid insoluble or thyroxin iodine

6 Another 50 gr of desiccated thyroid is ground with 10 cc distilled water

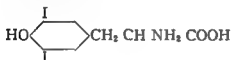
a Mixture is filtered

- (4) Concentration—same in blood and thyroid gland
- (5) Destruction is swift
- 2 Excretion of *thiouracil* (200 mg) in normal human⁸⁻¹¹
 - a Urine
 - (1) Detectable in 30 min
 - (2) Maximum in 1 to 2 hrs
 - (3) None in 48 hrs
 - b Blood (fasting)
 - (1) Detectable in 15 min
 - (2) Maximum in 30 min
 - c Feces—none

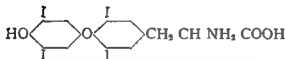
VII CHEMISTRY

A COLLOID

- 1 Each follicle contains different amounts
- 2 A thyroglobulin (molecular weight 700,000^{3, 4}) which yields two fractions in variable proportions (see below)
 - a "D" fraction (75%)—diiodotyrosine-like
 - b "T" fraction (25%)—thyroxine-like
- 3 Formulas of the two amino acids
 - a Diiodotyrosine



- b Thyroxine (synthesized)²



- 4 Physiologic activity of contents
 - a Thyroglobulin Active (more so than thyroxine)
 - b Thyroxine (dextro and levo) Both equally active
 - c Diiodotyrosine Inactive unless part of thyroglobulin molecule⁹

B THYROID HORMONE

- 1 Structure
 - Exact nature unknown the hormone is a portion of the colloid molecule
 - b Thyroid hormone or thyroglobulin

has not been demonstrated in the blood stream^{6, 16, 17}

- Discharged thyroid hormone may be peptide of 1 thyroxine
- d Diiodotyrosine comprises only 10 per cent of plasma iodine¹⁷
- Organic or plasma bound iodine may be index or indirect measure of circulating hormone in the blood
- 2 Daily output
 - Estimated secretion of thyroid hormone or its equivalent in thyroxine is 0.33 mg¹⁰
 - b The amount of desiccated thyroid needed by myxedematous adults is used as the basis for normal hormonal requirement
 - (1) Average maintenance dose is 1½ to 2 gr of desiccated thyroid (USP)
 - (2) 1½ gr of desiccated thyroid (USP) contains 220 gammas of iodine or 0.22 per cent of organic iodine
 - c It is not found in
 - (1) Urine
 - (2) Milk
 - (3) Sweat
- 3 Mode of action on end organs
 - a Unknown
 - b Catalytic (enzymic) action at cell surface suggested by Zondek^{18, 19}
- 4 Extrathyroidal deposits of thyroid hormone ("D" and "T" fractions of organic or colloidal iodine demonstrated)¹³
 - a Ovaries—may synthesize it, especially during pregnancy^{1, 8, 12}
 - b Muscles—concentration rises and falls with thyroid function^{1, 8, 12, 13}
 - c Liver¹³
 - d Intestines¹¹
 - Kidneys¹³
- 5 Blood stream—serum protein when iodinated in vitro and administered to humans relieves myxedema; this does not occur in vivo in humans,^{7, 14, 15} but may in animals⁵

VIII BIO ASSAY

- A INTRODUCTION—Tests to determine physiologic potency of
 - 1 Desiccated thyroid
 - 2 Thyroxine

- b Filtrate contains only inorganic iodine 5 cc used for quantitative analysis and should not exceed 10 per cent of total iodine
- c Residue containing iodothyroglobulin is
- (1) Physiologically active
 - (2) Used for standardization
- 7 Desiccated thyroid should contain 0.09 \pm 0.01 per cent of thyroxine iodine
- 8 U.S.P. standard—tablets must contain amounts of iodine not less than 0.17 per cent and not more than 0.23 per cent of the labeled amount of thyroid

F OTHER TESTS

- 1 Rate of
 - a Carbon dioxide production (mice)
 - b Oxygen consumption (rats)
- 2 Increased sensitivity of rats to oxygen deficiency may be used as an index

IX PATHOLOGY

A GROSS—See Tables 11 and 12

TABLE 12 THYROID DISEASES FOUND IN TOTAL NUMBER OF THYROID GLANDS EXAMINED (SURGICAL SPECIMENS) AT THE NEW ENGLAND DEACONESS HOSPITAL FROM 1927 THROUGH 1947 (DR SHIELDS WARREN)

Primary hyperplasia	10	26
Multiple colloid adenomatous goiter	10	964
Among these with secondary degenerative hyperplasia	1,586	
Colloid storage goiter		140
Adenomas	1,895	
Fetal		807
Simple		383
Embryonal		188
Colloid		160
Unclassified		125
Papillary cysts		102
Multiple		74
Yucc		33
Hurthle cell		23
Other benign tumors	43	
Cyst		33
Lipoma		13
Fibroma		7
Aberrant	33	
Lateral		31
Lingual		2
Inflammatory	362	
Thyroiditis acute and chronic		226
Hashimoto's struma		105
Piedel's struma		26
Tuberculois		5

Malignant	436	
Papillary cystadenoma		127
Papillary adenocarcinoma		80
Adenocarcinoma		67
Embryonal adenoma		28
Carcinoma simplex	116	
Small cell		80
Giant-cell		36
Carcinoma unclassified		13
Hurthle cell carcinoma		5
Miscellaneous cancers	10	
Epidermoid		4
Fibrosarcoma		3
Lymphoma		3
Various conditions		221
Total		74 00

B MICROSCOPIC AND HISTOPHYSIOLOGY

1 Experiments (animals)

a Thyrotropic hormone (TSH)²⁰

- (1) Excess (by injection) causes an increase in the thyroid gland of the

(a) Height and proliferation of the cells

(b) Mitochondria

(c) Golgi apparatus

(d) Absorption of iodides by the cells

(e) Cellular peroxidase and follicular colloid which hasten the processes listed above i.e. synthesis of diiodotyrosine and thyroxine

(f) Proteolytic enzyme which promotes²¹ "

{1} Secretion of colloid droplets into follicle

{2} Greater absorption of follicular colloid

(g) Colloid droplets at the base of the cells for release into the blood stream²²

- (2) Its inactivation (not destruction) by different thyroid biopsy specimens has been determined²³

TSH—UNITS

(a) Normal 3-4

(b) Hypofunction 0 (probably)

(c) Hyperplasia 7-8

(d) Single hypersecretory adenoma

TABLE 11 SURGICAL PATHOLOGY OF THE MORE COMMON DISEASES

SIZE	APPEARANCE	CAPSULE	CONSISTENCY	LOCATION	EXTENSION
Diffuse hyperplasia	Lobulated covered with veins reddish brown isthmus and pyramidal lobe always demonstrable	Tense held firmly	Elastic to firm	Normal	None always in the neck unless edematous changes extend into superior straight
Multiple nodular	Nodular cystic fibrotic bands between the lumps brown vascular variable but not marked	Tense intact	Variable in different parts of gland	Usual or rarely an intrathoracic aberrant thyrod	Into superior straight or mediastinum sometimes not invasive
Reddened struma	Asymmetrical gray color	Loose in parts tissue planes fused	Very hard	Normal	Adherent to trachea and muscles displaced with great difficulty
Hashimoto's struma	Diffuse bilateral contour of gland recognizable	Preserved	Firmer than normal	Normal	May surround trachea
Adenoma (single)	Asymmetrical variable color reddish brown if hemorrhage	Definite	Soft to hard	Any part of gland	Usually above superior straight
Adenoma with blood vessel invasion	As any adenoma (see above)	Intact	Soft to hard	Normal	Lungs and bones
Papillary carcinoma	May be cystic or hemorrhagic	May be broken	Firm	In lateral areas of thyroid	May be adherent to muscle
Diffuse carcinoma	Vascularly increased white	Invasion marked	Hard	Neck superior to aight omid (normal)	Adherent to muscle via on of fascia lymphatic nodes

- (2) Proteolytic and cytochrome oxidase enzymes are unaffected as hormone is discharged until exhausted
- (3) Marked hyperplasia of thyroid cells
- (4) Vascularity increased
- (5) Involution with colloid storage takes place if iodine is given in sufficient amounts but new hormone is not made or secreted¹
- (6) Radioactive iodine is inhibited⁶ and prevented from penetrating follicles⁹ ~ 62-61
- (7) Prolonged administration produced histologic appearance of adenocarcinoma in rats⁷⁷ 53
- e Sulfonamides¹ 0
 - (1) Competitive attachment of these drugs to liberated iodine (see below) preventing synthesis of
 - (a) Diiodotyrosine
 - (b) Thyroxine
 - (2) Peroxidase increased in cells but not in colloid
 - (3) Other enzymes are not depressed
- f Potassium thiocyanate (when given over prolonged periods to susceptible individuals) (see Fig 118)
 - (1) Myxedema may develop
 - (2) Mild hyperplasia produced
 - (3) Conversion of iodine to D and T fractions depressed
 - (4) Gland takes up 76 per cent of tracer doses of radioactive iodine
 - (5) Iodine administration will prevent goiter in animals
- g Various other agents on thyroid slices
 - (1) Inhibit formation of D and T fractions
 - (a) Cyanide
 - (b) Azide
 - (c) Sulfides
 - (d) Carbon monoxide
 - (e) Sulfonamides
 - (f) Iodides
 - (g) Thiourea
 - (h) Thiouracil
 - (i) Allyl thiourea
 - (j) Para aminobenzoic acid
 - (k) Potassium thiocyanate
 - (2) Prevent uptake of iodine
 - (a) Cyanide
 - (b) Sulfides
 - (c) Potassium thiocyanate
 - (3) Do not prevent iodine accumulation
 - (a) Sulfonamides
 - (b) Thiourea
 - (c) Thiouracil
 - (d) Allyl thiourea
 - (e) Para aminobenzoic acid
- h Nerve stimulation (superior laryngeal)—increase in⁷
 - (1) Cellular height
 - (2) Mitochondria
 - (3) Golgi apparatus
 - (4) Vacuoles
 - (5) Hormone discharge

(Findings are not conclusive inasmuch as stimuli may reach pituitary or adrenals both of which can cause such changes)
- i Hypophysectomy¹⁰
 - (1) Results—decrease in
 - (a) Cellular height
 - (b) Mitochondria
 - (c) Golgi apparatus
 - (d) Absorption of iodides
 - (e) Proteolytic enzyme (see above)
 - (2) Peroxidase may not be affected because diiodotyrosine fraction is synthesized (although not the thyroxine fraction)⁶⁴ 70
 - (3) Colloid stored in follicle relatively inactive (D fraction)
 - (4) Less than normal amounts of thyroxine in thyroid gland⁶⁴ 70
- j Miscellaneous
 - (1) Inanition produces same effects as hypophysectomy⁶⁹
 - (2) High protein diet does not cause thyroid hypertrophy this may be factor in production of thyroid deficient pigs³³ 44 67
- 2 Clinical states
 - a Colloid adenomatous goiter with euthyroidism
 - (1) Epithelium
 - (a) Inactive mostly
 - (b) Active portion has colloid droplets only at apex

- [1] Hyperplastic portion 7 8 TSH—UNITS
- [2] Atrophic section Less than 1
- (3) Essential to form goiter⁶
- b Iodine in excess (therapeutic amounts)
- (1) Thyrotropic hormone^{1 13 4}
39 49 60 61
- (a) Inactivation usually
- (b) Pituitary content increased (with large doses)
- (2) Thyroid^{13 17 19}
- (a) Proteolytic enzyme may be decreased directly or indirectly through the pituitary
- (b) Absorption of intrafollicular colloid by the cells for hormone synthesis and secretion is decreased
- (c) Peroxidase is not affected
- (d) Colloid (with involution) is
- [1] Synthesized continually
- [2] Transferred to follicle
- [3] Trapped there
- c Radioactive iodine (orally administered)^{6 11 30 31 3 3 4 47}
- (1) Uptake by thyroid varies with the following
- (a) Dosage
- (b) Previous iodination
- (c) Ingestion of desiccated thyroid
- (d) Degree of secretory activity
- (e) Type of gland⁶⁰
- (f) Presence of antithyroid medication in gland as well as type of drug
- (g) Other factors
- [1] Stress
- [2] Diet
- [3] Exposure to cold
- (2) Location of trapped radioactive iodine
- (a) Largest amount found in colloid of
- [1] Hypersecretory hyperplastic thyroid
- [2] Diffuse colloid goiter with euthyroidism
- (b) Greatest amount in cells of

goiter associated with hypothyroidism

- (c) Adenomas take up less than surrounding tissue in non-toxic nodular goiter

(3) Radioactive iodine studies do not correlate well with degrees of clinical hyperthyroidism¹³

(4) Résumé of absorption and urinary excretion in normal subjects and various types of thyroid disease (only approximate values can be outlined as dosages and methods of experiments differ—see Table 13, Charts 28 and 29)

TABLE 13 RADIOACTIVE IODINE ADMINISTRATION^{3 7 1 28 29 31 32, 37 40 43 60 65 68}

TYPE OF THYROID GLAND	PER CENT OF ABSORPTION BY THYROID	PER CENT OF URINARY EXCRETION WITHIN 48 HRS
Normal	20-40	60-80
Hypersecretory diffuse hyperplastic*		
Untreated	80-90	10-20
Iodine treated	1-7	85-95
Thiouracil prepared	10-20	80-90
Nodular goiter		
Toxic no iodine	3-7	85-90
Nontoxic	10-20	49-75
Myxedema		
Without goiter	?	75-80
With goiter	Probably 10-20	49-75
Surgical	0	80-90
Thyroiditis	Diminished	
Cancer (15%)	Variable	

* In view of the differences in urinary iodine in hypersecretory hyperplastic thyroid of short duration (greater) and of long duration (less) it is obvious that the output of iodine in these experiments would be influenced by this phenomena

d Thiouracil (see Fig 119)^{4 5 8 1 18}
41 4 50 6 7 61 63 71

- (1) Peroxidase system is depressed thus retarding
- (a) Liberation of free iodine
- (b) Synthesis of hormone (diiodotyrosine and thyronine formation prevented none in cells or colloid)

- (b) Thyroid cells show changes depending on their state of function
- (2) Nodules which appear functionally autonomous and not hypersecretory
 - (a) Colloid has less iodine and thyroxin fraction than surrounding tissue
 - (b) Cont nt mostly diiodotyrosine factor
 - (c) Surrounding tissue is hyperplastic and source of excess hormone
 - (d) Radioactive iodine taken up slowly⁴³
 - (e) Fetal adenoma also less active⁴³
- (3) Nodules which appear partially hypersecretory
 - (a) As the disorder progresses periphery of adenoma may have
 - [1] Colloid loss
 - [2] Hormone secretion in excess
 - (b) Entire adenoma finally may be hypersecretory with typical hyperplasia
 - (c) Iodine may penetrate adenoma causing colloid storage in periphery a reversal of the process by which it becomes hypersecretory
 - (d) Thyroxin fraction presumably increased⁴⁴
- (4) Hypersecretory discrete nodule or nodules with surrounding atrophic thyroid tissue
 - (a) Radioactive iodine taken up more readily⁵⁴
 - (b) Iodine has less therapeutic value possibly because of dense capsule which retards penetration
 - (c) Adenomatous tissue shows
 - [1] Twice the power to inactivate thyrotropic hormone than does normal tissue
 - [2] Similarity to hyperplastic tissue

- [3] An increase in
 - [a] Thyroxin fraction
 - [b] Proteolytic enzyme
- (d) Removal restores normal basal metabolic rate

X CLASSIFICATIONS

I COMPREHENSIVE LIST OF CHIEF FACTORS IN ENDOCRINE DISEASES—see 2 X A

II HORMONAL

1 Introduction

- a The hormonal status in thyroid disease may vary from hypofunction to hyperfunction in the same individual depending on the natural course of the disorder
- b For example the development of hyperthyroidism in a goitrous cretin from therapy
- c Any hormonal classification therefore refers only to the situation at hand

2 Normal—euthyroidism

3 Hyposecretion

- a Cretinism
- b Myxedema

4 Hypersecretion—hyperthyroidism

C CLINICAL

1 Introduction

- a Thyroid function may bear little relationship to the type of disease present within the gland except when thyroid tissue is absent or profoundly deficient
- b Generally however there is clinical correlation

2 Euthyroidism

- a Normal thyroid function with or without thyroid enlargement of any type
- b Exophthalmic syndrome

3 Cretinism

- a At or before birth
 - (1) Congenital absence of thyroid—synonyms
 - (a) Congenital athyreosis
 - (b) Thyroaplasia
 - (c) Sporadic cretinism without goiter
 - (2) Congenital goiter
 - (3) Endemic goiter
- b Infancy and childhood
 - (1) Congenital goiter

- (2) Colloid may be
 - (a) Deficient in thyroxin factor
 - (b) Inactive
 - (3) Mitochondria and Golgi apparatus
 - (a) Are decreased
 - (b) May go into follicle
 - (4) Peroxidase granules are not increased
 - (5) Proteolytic enzyme is less active in these cells, permitting colloid secretion into follicle, but not reabsorption^{15 17}
 - (6) Thyroid administration may decrease glandular size
 - (7) Iodine may cause thyroid deficiency by³⁹
 - (a) Increasing storage
 - (b) Decreasing hormone secretion
- b Myxedema**
- (1) Atrophy of thyroid gland
 - (a) Few follicles may remain, some of which are hyperplastic
 - (b) Scar tissue
 - (c) Hyaline degeneration
 - (d) Lymphocytic infiltration
 - (e) Hormone is insufficiently synthesized
 - (f) Radioactive iodine uptake does not occur
 - (2) Thyroiditis of various types—replacement of follicles by lymphoid or sclerotic tissue
 - (3) Colloid adenomatous goiter
 - (a) Fetal adenoma may be present with or without some hyperplastic follicles
 - (b) Colloid follicles with flattened epithelium are numerous
 - (c) All normal uninvolved tissue may be
 - [1] Greatly compressed
 - [2] Nonfunctioning (no actual data here)
 - (4) Diffuse enlargement (clinically colloid or hyperplastic large follicle hyperplasia)⁴³
 - (a) Colloid secretion into follicles
- (b) Epithelial
 - [1] Hyperplasia
 - [2] Proliferation
 - (c) Hormonal output in variable amounts (see 17)
 - (d) Thyroid administration
 - [1] Myxedema relieved if present
 - [2] Gland may decrease in size, possibly through
 - [a] TSH inhibition
 - [b] Decreased hyperplasia
 - (e) Iodine administration
 - [1] Hormonal secretion may be decreased, if normal previously (rare)
 - [2] Myxedema may follow (infrequent)
 - [3] Basal metabolic rate rise has been reported²⁸
 - [4] Gland itself will take up radioactive iodine
- c Hyperthyroidism (hypersecretory diffuse hyperplastic thyroid)**
- (1) Changes are present ■ noted under histology due to hypersecretion (see 14 V C 2)
 - (2) Cells
 - (a) Number—increased
 - (b) Colloid particles—larger
 - (c) 'Vacuoles' in basal portion as compared with apex, suggest greater hormone synthesis and secretion (reversal of polarity)
 - (3) Colloid in follicles may be completely reabsorbed but central portion of the remaining colloid in other follicles may stain dark before complete absorption (indicating thick concentrated colloid—see Fig 120)
 - (4) There is an increase in
 - (a) Vascularity of interfollicular tissue
 - (b) Proteolytic enzyme of follicle^{1 18}
 - (c) Peroxidase activity
- d Nodular goiter with hyperthyroidism**
- (1) Introduction
 - (a) Histologic picture may be divided into three main groups

XI and XII CHIEF CLINICAL FINDINGS OF HYPOSECRETION AND HYPERSECRETION

	HYPOSECRETION (PRIMARY THYROID DEFICIENCY, NOT FROM ABSENT TSH)	HYPERSECRETION (FROM EXCESS TSH, TH OR DESICCATED THYROID)
PHYSICAL STATUS		
Appearance	Lethargic, bloated	Apprehensive 'frightened look
Age	Any	Any
Mental response	Poor, slow	Quick, alert
Weight	Variable	Evidence of emaciation may be severe
Integument		
Texture	Scaling, wrinkled, rough	Smooth, delicate
Temperature	Cool	Warm
Moisture	Dry	Excessive
Nails	Brittle, thick	Fissures, undergrooved
Hair		
Head	Dry, brittle, often fine, falls out easily	Normal
Sexual	Normal, scant or absent	Normal or decreased
Eyes		
General	Puffiness of lids, watery	Normal, stare or exoph thalmos
Palpebral fissures	Narrow	Wide
Muscles	Normal	Paralyses may occur
Voice		
Voice	Hoarse, deep	Normal
Speech		
Speech	Slow, deliberate	Quick, talkative
Thyroid gland		
Thyroid gland	Not palpable usually	Enlarged in majority
Heart		
Rate	Bradycardia	Tachycardia
Output	Decreased	Increased
Tonus	Decreased	Decreased
Irritability	Decreased	Increased
Circulation		
Peripheral	Decreased	Increased
Time	Increased	Decreased
Blood		
Pressure	Decreased	Increased
Flow	Decreased	Increased
Volume	Decreased	Increased
Movements		
Movements	Slow, awkward	Hasty, restless
Bone		
Growth (in young)	Retarded	Accelerated
Density	Increased	Decreased
Maturation	Decreased	Increased
Muscles		
Muscles	Normal	Normal or atrophy

- (2) Colloid or colloid nodular goiter (endemic)
- (3) Hyposecretory diffuse hyperplastic goiter
- (4) Thyroid atrophy
- (5) Thyroiditis
- (6) Surgical ablation
- 4 Myxedema
 - a Synonyms
 - (1) Gull's disease
 - (2) Primary thyroid
 - (a) Deficiency
 - (b) Atrophy
 - (3) Hypothyroidism
 - (4) Athyreosis
 - b Colloid or colloid nodular goiter (endemic)
 - c Hyposecretory diffuse hyperplastic goiter
 - d Thyroiditis
- 5 Hyperthyroidism
 - a Hypersecretory diffuse hyperplastic goiter—synonyms
 - (1) Parry's disease
 - (2) Graves's disease
 - (3) Basedow's disease
 - (4) Exophthalmic goiter
 - (5) Primary hyperthyroidism
 - (6) Thyrotoxicosis
 - (7) Toxic hyperplastic goiter
 - b Nodular goiter and superimposed hypersecretory hyperplasia in remainder of gland, synonym—adenomatous or nodular goiter with superimposed Graves's disease or secondary hyperthyroidism
 - c Hypersecretory nodular goiter—synonyms
 - (1) Adenomatous goiter with hyperthyroidism
 - (2) Nodular goiter with hyperthyroidism
 - (3) Multiple colloid adenomatous goiter with hyperthyroidism
 - (4) Toxic nodular goiter
 - (5) Toxic adenomatous goiter
 - d Hypersecretory solitary nodule within a hyposecretory gland—synonyms
 - (1) Hyperfunctioning adenoma
 - (2) Hyperfunctioning solitary nodule
 - (3) Toxic adenoma
 - (4) Plummer's disease
 - e Factitious—synonyms
 - (1) Self induced
 - (2) Alimentary
 - (3) Thyrotoxicosis factitia
 - f Coincidental disease of thyroid gland with superimposed hypersecretory hyperplasia
 - g Recurrent or persistent
 - (1) Hyperthyroidism—any type
 - (2) Colloid goiter
 - (3) Nodular goiter
 - h Thyrocardiac disease—any type of hyperthyroidism

D TUMORS

1 Benign

- a Colloid
 - (1) Goiter
 - (2) Nodular (or endemic) goiter
 - (3) Cyst
- b Diffuse normosecretory hyperplastic goiter
- c Thyroiditis
 - (1) Nonspecific
 - (2) Hashimoto
 - (3) Riedel
 - (4) Amyloid
 - (5) Syphilitic
 - (6) Tuberculous
- d Lingual thyroid
- e Lateral aberrant thyroid
- f Adenoma
 - (1) Fetal
 - (2) Embryonal
 - (3) Simple
 - (4) Multiple
 - (5) Hurthle cell

2 Malignant

- a Benign metastasizing
- b Malignant adenoma
- c Papillary adenocystoma
- d Papillary adenocarcinoma
- e Carcinoma
 - (1) Simplex
 - (2) Alveolar
 - (3) Giant cell
 - (4) Hurthle cell
- f Metastatic nodule—extrinsic
- g Miscellaneous types

	HYPOSECRETION (PRIMARY THYROID DEFICIENCY NOT FROM ABSENT TSH)	HYPERSCRETION (FROM EXCESS TSH, TH OR DESICCATED THYROID)
Protein		
Total serum	Normal or increased	Normal or decreased
Albumin	Normal or decreased	Decreased
Globulin	Normal or decreased	Normal or increased
Spinal fluid	Increased	Decreased
Phosphatase (alkaline growth phase)	Decreased	Increased
Phosphorus		
Blood	Normal or decreased	Normal or increased
Urinary	Decreased	Increased
TSH (urinary thyrotropic hormone—see Chart 30)		
Active	Increased	Decreased or absent
Inactive	Absent	Increased
Specific dynamic action of protein	Decreased (or absent)	Variable
Sugar		
Blood	Normal or decreased	Variable
Tolerance	Increased	Variable
Urinary	Absent	Absent or increased
Urea (blood)	Decreased	Increased
Water		
Excretion	Decreased	Increased
Retention	Increased	Decreased

SYMPTOMATOLOGY

Neuromuscular and sensory		
Fatigue	Usual	Marked
Heat	Tolerance	Intolerance
Memory	Poor	Alert
Nervousness	None	Marked
Sleepiness	Common	None
Sweating	None	Marked
Tremor	None	Present
Cardiovascular		
Angina of effort	May occur	May occur
Dyspnea	May be present	Often present
Palpitation	None	Common
Gastro intestinal		
Appetite	Anorexia	Polyphagia
Bowel movements	Normal or constipation	Normal or diarrhea
Weight	Gain	Loss
Genito urinary		
Menses	Amenorrhea or menorrhagia	Normal, amenorrhea or oligomenorrhea

	HYPOSECRETION (PRIMARY THYROID DEFICIENCY, NOT FROM ABSENT TSH)	HYPERSECRETION (FROM EXCESS TSH TH, OR DESICATED THYROID)
LABORATORY DATA		
Alimentary tolerance for glucose	Increased	Decreased
Absorption through gastro intestinal tract (probably all substances capable of absorption)	Decreased	Increased
Adrenalin response	Decreased	Increased
Androgens (17 ketosteroids)	Decreased	Normal and decreased
Basal metabolic rate	Decreased	Increased
Calcium		
Bone	Increased	Decreased
Fecal	Decreased	Increased
Serum	Normal	Normal
Urinary	Decreased	Increased
Cholesterol		
Esters	Increased	Decreased
Destruction	Increased	Decreased
Free	Increased	Decreased
Creatine		
Blood	Decreased	Normal or increased
Dietary	Decreased	Increased
Urinary	Decreased	Increased
Tolerance	Increased	Decreased
Estrogens	Normal	Normal
FSH (urinary follicle stimulating hor- mone)	Negative, occasionally positive	Negative, occasionally positive
Glycogen		
Glycogenolysis	Decreased	Increased
Liver	Increased	Decreased
Hematology		
Hemoglobin	Normal or decreased	Normal or decreased
Red blood cells	Normal or decreased	Normal (rarely increased or decreased)
White blood cells	Normal or decreased	Variable
Iodine		
Inorganic	Decreased	Increased
Organic	Decreased	Increased
Total	Decreased	Increased
Urinary	Decreased	Increased
Insulin sensitivity	Decreased	Increased
Lipids (blood)	Increased	Decreased
Nitrogen		
Excretion	Decreased	Increased
Retention	Increased	Decreased

- [6] Irregular
 - [7] Pebbly
 - (c) Size—each normal lobe (average)
 - [1] Length— $1\frac{1}{2}$ in
 - [2] Thickness— $\frac{1}{2}$ in
 - (d) Location
 - [1] Normal
 - [2] Substernal
 - [3] Intrathoracic
 - [4] Aberrant
 - (e) Fixation to surrounding structures
 - (f) Other lumps in neck
 - (g) Tracheal displacement by goiter—laryngeal prominence of thyroid cartilage should be in midline normally
 - (h) Thrills which may be present
 - c Auscultation—bruits may be heard
 - d Stridor (see Fig 122)
 - (1) Present in some with abnormal position of head
 - (2) Anterior compression may be demonstrated with forward flexion of the head
 - (3) Lateral compression may be found when head is bent or turned to either side
 - e Measurement of size—neck circumference may be used as an index but
 - (1) Difficult to determine accurately
 - (2) Unreliable for minor changes
 - f Transillumination—cystic nature of thyroid nodules may be revealed
 - 4 Vocal cord examination—this should be done for possible laryngeal nerve paralysis
 - 5 Neuromuscular system in hyperthyroidism
 - a Tremor—fine type of
 - (1) Extremities
 - (2) Whole body occasionally
 - b Quadriceps weakness
 - (1) Leg test (Lahey)¹¹
 - (a) Method
 - [1] Patient sits forward on edge of chair
 - [2] His arms are dropped to the sides, and his hands should be free
 - [3] One leg is then raised parallel with the floor
 - [4] An attempt is made to hold it for 1 min
 - (b) Results
 - [1] Negative
 - [a] Normal person has little difficulty in keeping leg in this position for 1 min
 - [b] Some patients give up shortly and voluntarily drop the leg especially nervous individuals without hyperthyroidism
 - [2] Positive
 - [a] Patient cannot prevent a gradual lowering of his leg
 - [b] Tremor usually increases as his leg slowly sinks to the floor
- (2) Chair test (Plummer)
 - (a) Method
 - [1] Patient puts one foot on seat of a low chair
 - [2] He tries to raise himself onto it
 - (b) Results
 - [1] Negative—easily performed
 - [2] Positive—patient cannot accomplish this without using his arms in pulling himself up
- 6 Cardiovascular system
 - a Pulse
 - (1) Myxedema
 - (a) Bradycardia
 - (b) Normal
 - (2) Hyperthyroidism
 - (a) Tachycardia usually
 - (b) Irregular (10%)
 - (c) Forceful or bounding with rapid collapse in diastole
 - b Blood pressure
 - (1) Myxedema
 - (a) Variable
 - (b) Nothing characteristic

XIII EXAMINATION OF PATIENT**A HISTORY****1 Abnormal function**

a Diagnosis of hypersecretion or hyposecretion can often be made from the history alone

b Hyposecretion

- (1) Sluggishness
- (2) Somnolence
- (3) Sensitivity to cold
- (4) Dryness of skin
- (5) Weight gain in some
- (6) Growth retardation (children)

c Hypersecretion

- (1) Weight loss with adequate food intake
- (2) Palpitation
- (3) Sensation of warmth
- (4) Tremor
- (5) Nervousness
- (6) Sweating

2 Tracheal compression

a Dyspnea associated with stridor

b Development may be

- (1) Gradual
- (2) Sudden (hemorrhage into goiter)

3 Malignancy

a Thyroid gland may grow rapidly

b Pressure symptoms

c History of comparatively little value

4 Thyroiditis

a Acute febrile state

b Thyroid

- (1) Tenderness
- (2) Swelling
- (3) Pain (present or past) is often noted on swallowing

B PHYSICAL STATUS**1 Appearance and behavior**

a Myxedema

- (1) Facial expression dull
- (2) Bloated appearance often
- (3) Speech slow
- (4) Behavior sluggish

b Hyperthyroidism

- (1) Restless
- (2) Alert
- (3) Nervous
- (4) Frightened ('frozen fright')

2 Eye signs

a Myxedema

- (1) Gaze impassive

(2) Puffiness, transparent edema below and lateral to lids in some cases

(3) Palpebral fissures narrow

b Hyperthyroidism

(1) Stare

(2) Exophthalmos

(3) Lid retraction

(4) Lack of convergence

(5) Ocular palsy or palsies

(6) Puffiness

3 The thyroid gland

a Inspection for

(1) Enlargement

(a) Unilateral

(b) Bilateral

(2) Contours

(a) Uniform

(b) Nodular

(c) Irregular

(3) Location

(4) Veins of neck and/or chest and abdomen which may show

(a) Distention

(b) Pulsations

(c) Tortuosities

(5) Other lumps in the neck

(a) Lymph glands

(b) Lateral aberrant tissue

(c) Thyroglossal cyst

(d) Branchial cyst

b Palpation (see Fig 121)

(1) Method

(a) Left sternocleidomastoid muscle is relaxed by turning the head to right or vice versa

(b) Displace the thyroid cartilage with the thumb from left side

(c) Thumb and middle finger of other hand firmly grasp thyroid lobe on the right side

(d) Patient swallows

(2) Examination for

(a) Tenderness

(b) Consistency

[1] Firm

[2] Soft

[3] Hard

[4] Smooth

[5] Nodular

- (a) More resistant to desiccated thyroid medication
 - (b) Cholesterol free diet is not as effective in producing a decrease
- 2 Iodine (see 103 IX.)
- a Urinary (see 26 XI 10 Table 13 34 IX 4 103 IX.)
 - (1) Excretion has clinical significance chiefly in detection of factitious hyperthyroidism
 - (2) Same precautions as for collection of blood for total iodine
 - (3) Results over 800 to 1 000 micrograms/24 hrs indicate ingestion of desiccated thyroid (or iodine)
 - b Blood (see Chart 33)
 - (1) Comment
 - (a) Total blood iodine is a fair index of circulating thyroid hormone when collected under certain strict precautions since it is subject to easy change from
 - [1] Diet
 - [2] Medication
 - [3] Contamination
 - (b) Protein bound iodine is the best chemical measure of thyroid hormone in the blood and is little affected by diet or contamination but may be by ingestion of large quantities of iodine preparations²³
 - (2) Interpretation
 - (a) Total blood iodine—in absence of factors other than excess thyroid hormone a high level = corroborative evidence of hyperthyroidism
 - (b) Protein bound iodine
 - [1] Borderline values are of little diagnostic significance
 - [2] Increased values usually indicate hyperthyroidism except in pregnancy
 - [3] Normal (or almost) levels are possible as for total iodine in severe and long standing hyperthyroidism
- 3 Basal metabolic rate
- a Preparation of patient
 - (1) No food 12 hrs preceding test
 - (2) Sips of water may be allowed
 - (3) A comfortable night's sleep is desirable, sedatives are indicated for restlessness
 - (4) Emotional disturbances must be avoided preceding test, otherwise test should be postponed
 - (5) Check temperature, defer procedure if elevated
 - b Place of test
 - (1) Overnight stay at place of test desirable results run 10 per cent lower under these circumstances
 - (2) If above not possible travel to place of test should be with least possible effort
 - (3) Patient should rest in reclining position at least 20 to 30 min before procedure
 - (4) Surroundings should be
 - (a) Quiet
 - (b) Restful
 - c Technician qualifications of
 - (1) Accuracy
 - (2) Poise
 - (3) Tact
 - (4) Kindness
 - (5) Patience
 - d Important technical points
 - (1) Replace soda lime frequently
 - (2) Check apparatus for leaks
 - (3) Adjust nose clip comfortably
 - (4) Do not remove false teeth
 - (5) Be suspicious if
 - (a) Pulse rate is low
 - (b) Oxygen consumption appears rapid
 - (6) Recalculate all tests for confirmation
 - e Interpretation
 - (1) Normal test
 - (a) The concept of what constitutes this is somewhat in definite, although minus 15 per cent to plus 5 per cent is average
 - (b) The metabolic trend on repeated tests on subsequent days is more reliable because of

(2) Hyperthyroidism

(a) Pulse pressure of 60 mm or more

(b) Diastolic pressure usually below 80 mm (unless co incident hypertension)

(c) Diastolic pressure may be read as zero, simulating a true Corrigan pulse of aortic insufficiency

[1] To distinguish between the two, the stethoscope is placed so that the distal rim of the diaphragm is pressed firmly against the artery (method of Blumgart)⁴

[2] Higher level of diastolic pressure will then be found unless aortic insufficiency is also present

C LABORATORY DATA

1 Cholesterol (plasma or serum)

2 Iodine

a Urine

b Blood

3 Basal metabolic rate

4 Urinary thyrotropic hormone—analyses impractical for routine use

D METHODS FOR SPECIAL PROCEDURES

1 Cholesterol (serum or plasma)⁷ (see 103 III Charts 31 and 32)

a Fasting state unnecessary for collection of blood samples

b Average values

	mg %
(1) Normal	180

(a) Children have lower values

(b) Older age groups show higher levels

(2) Myxedema 300

(3) Hyperthyroidism 140

(4) Panhypopituitarism 200

(5) Hypometabolism 180

c Interpretation

(1) Myxedema and cretinism

(a) High readings

[1] Result of thyroid deficiency (other causes excluded) more often than is a basal meta

bolic rate below minus 20 per cent

[2] Association with a low basal metabolic rate increases the possibility of the diagnosis but may be found in apparently normal individuals

(b) Upper normal values do not eliminate either one⁴

(c) Clinical evidence is important, but if lacking a therapeutic trial of desiccated thyroid may be worth while (see 25 XVI C)

(2) Hypersecretory diffuse hyperplastic thyroid

(a) Low levels which are proportional to the basal metabolic rate elevation is less striking than the reverse relationship in myxedema

(b) Usefulness in diagnosis is limited

(c) Trend during treatment may be of some value

(3) Hypercholesterolemia—other causes

(a) Of 404 individuals suspected of having a high plasma cholesterol for various reasons (including thyroid deficiency) 65 per cent had thyroid deficiency⁷

(b) Therefore the probable chance of a high cholesterol indicating thyroid deficiency regardless of clinical findings, is 2 in 5

d Diagnostic response to treatment

(1) Myxedema

(a) Desiccated thyroid administration (not over 2 gr per day) produces a striking fall (usually 50%)

(b) Marked drop with cholesterol free diet but adequate in calories without thyroid treatment

(2) Hyperthyroidism—reciprocal rise in majority of cases with fall in basal metabolic rate

(3) Hypercholesterolemia—other causes

- (6) Metal airway attached to rubber mouthpiece whenever breathing is not free
 - (7) Adhesive tape applied around rubber mouthpiece and mouth to prevent leakage of air
 - (8) Chin supported to facilitate breathing
 - (9) Additional pentothal given if needed, hyperthyroid patients require larger doses than others
- Interpretation
- (1) Elevated readings
 - (a) Hyperthyroidism—all types
 - (b) Acromegaly
 - (c) Pheochromocytoma
 - (d) Aortic stenosis
 - (2) Normal in
 - (a) Parkinson's disease
 - (b) Spasmodic torticollis
 - (c) Nervous states
 - (d) Hypertension
- 5 Thyrotropic hormone assays (see 14 VIII)
- a Comment
 - (1) Extremely difficult procedure
 - (2) Limited clinical value
 - (3) Inactivated hormone is reactivated by reducing agents
 - b Normal
 - (1) Urine—about 2 Junkmann Schoeller units per day¹²
 - (2) Blood—negative or 0.005 to

0.0025 Junkmann Schoeller units (results depend on the type of test)⁵

- c Hypothyroidism (urine and blood)
 - (1) Active—positive
 - (2) Inactive—absent
- d Hyperthyroidism (urine and blood)
 - (1) Active—absent
 - (2) Inactive—present

E ROENTGENOGRAMS AND FLUOROSCOPY

- 1 Trachea (using Bucky diaphragm)
 - a Views
 - (1) Anteroposterior
 - (2) Oblique
 - (3) Lateral
 - b Indication—to determine degree of tracheal compression
- 2 Esophagus for involvement by extension of thyroid malignancy
- 3 Chest
 - a Substernal or mediastinal shadow
 - b Movement of substernal mass on swallowing
 - c Tracheal deviation
 - d Metastatic lesions
 - e Motion of diaphragm
 - f Congestive failure
 - g Heart
 - (1) Size
 - (2) Contour
 - (3) Contractions
 - (4) Rate
 - (5) Rhythm

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- [1] Unfamiliarity with procedure
- [2] Apprehension
- (2) Myxedema
- (a) A low level (minus 20% or below) is usual^{7, 9}
- (b) Occurrence only 2 out of 5 people with readings of minus 20 per cent or lower
- (3) Hypersecretory hyperplastic gland (untreated)
- (a) Results of plus 20 per cent or over are commonest
- (b) Rare exceptions when an individual's normal rate is low (about minus 20% or below) before onset of the disease, then the readings may be only plus 5 per cent or so
- (c) A high rate is not diagnostic per se, because evidence of the disorder must also be present
- f High readings, exclusive of hypersecretory nodular or hyperplastic thyroids⁶
- (1) Factitious hyperthyroidism
- (2) Acromegaly
- (3) Cushing's syndrome
- (4) Pheochromocytoma
- (5) Diabetes mellitus (in acidosis)
- (6) Blood dyscrasias
- (a) Leukemia (lymphatic or myelogenous)
- (b) Polycythemia vera
- (c) Pernicious anemia
- (d) Splenic anemia
- (7) Aortic stenosis^{9, 10, 11}
- (8) Congestive heart failure
- (9) Malignant or severe hypertension
- (10) Pregnancy (last few weeks and during lactation)
- (11) Fever
- (12) Certain individuals never can adapt themselves to this test so trial of oral sedation to point of drowsiness is indicated
- Low readings, exclusive of myxedema⁶
- (1) Normal
- (2) Panhypopituitarism
- (3) Adrenal insufficiency
- (4) Hypogonadism
- (5) Prolonged inactivity, i.e., bed ridden patients
- (6) Chronic malnutrition from any cause
- (7) Anorexia nervosa
- (8) Psychotic states or variety of diseases of nervous system, i.e.
- (a) Severe mental depression
- (b) Schizophrenia
- (c) Psychoneurosis
- (9) Amputation of extremities
- (10) Nephrotic syndrome
- (11) Idiopathic
- (12) Miscellaneous

TABLE 14 HYPOMETABOLISM (BMR—12% OR BELOW) IN 308 CASES⁹

CAUSE	Pzr Cnt
Idiopathic	330
Clinical myxedema (usually below minus 25%)	61
Miscellaneous	609

4 Basal metabolism test under pentothal anesthesia (see Chart 34)

a Indications

- (1) Elevated basal metabolic rate without evidence of hyperthyroidism
- (2) Determination of true basal metabolic rate in hyperthyroidism when associated with other causes for an elevated reading (see below)

b Method

- (1) Trained anesthetist should prepare patient
- (2) Atropine sulfate gr 1/150 subcutaneously, 1 hr before procedure
- (3) Throat sprayed with 10 per cent cocaine solution a few minutes before test
- (4) Sodium pentothal solution injected intravenously using smallest amount to produce complete relaxation
- (5) Rubber mouthpiece inserted if breathing is unhampered

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FIG 115 CAMERA LUCIDA DRAWINGS OF INTACT RAT THYROID AFTER INJECTION OF TSH (de Robertis) (Top left and center) Thirty min after injection of TSH Colloid particles are being extruded from cell into alveolus (Top right) Reversal of polarity 3 hrs after injection of TSH Colloid is now being resorbed. (Bottom) Six hrs after TSH Colloid is accumulating in cells and particles appear to be migrating to base of cell losing their density This movement is thought to precede actual secretion into capillaries at base of cell Note change in contour of cell (de Robertis E. Cytological and cytochemical basis of thyroid function Tr New York Acad Sc 50 317-335)

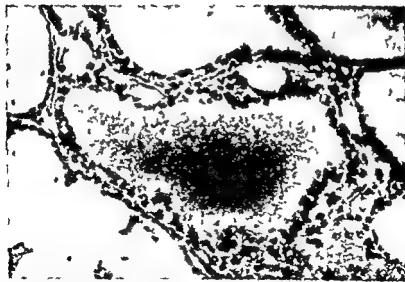
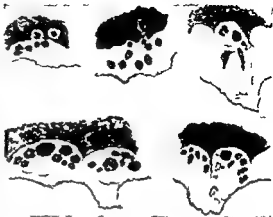


FIG 116 RADIOACTIVE IODINE IN NORMAL THYROID GLAND (See also Fig 123) Normal thyroid gland showing concentration of radioactive iodine in colloid of some follicles This demonstration verifies the concept that under normal conditions only a few follicles are active whereas others are in a resting state The smaller follicles are apt to show the greatest activity by a greater uptake of isotope Note that the epithelium appears to be higher than in the adjoining follicles where little or no radioactive iodine has been deposited. (Fitzgerald, P J and Foote F W Jr The function of various types of thyroid carcinoma as revealed by the radioautographic demonstration of radioactive iodine J Clin Endocrinol 9 1155-1170)



FIG 113 THYROID GLAND This specimen demonstrates the shape of the thyroid and the pyramidal lobe. Actually, it is the hyperplastic gland of Graves's disease removed in total at operation.

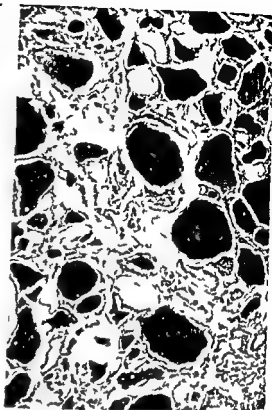


FIG 114 THYROID Normal adult thyroid gland

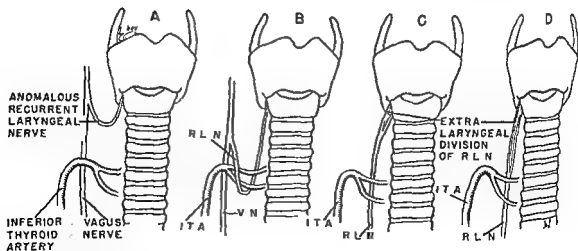


CHART 27 RECURRENT LARYNGEAL NERVE (RIGHT) SHOWING ANOMALOUS DISTRIBUTIONS. In C and D the nerve is in its usual position but divides before entering larynx (Lahey F H Exposure of the recurrent laryngeal nerve in thyroid operations further experiences Surg Gynec & Obst 78 239 244)

CHART 29 (Right) URINARY EXCRETION OF RADIOIODINE IN MYXEDEMA Greater amounts of radioiodine are excreted in the urine of myxedematous patients (total 6) and a longer period of time is required to reach a plateau. For comparison the composite curve of normal men is illustrated (Kistling F R Jr, Power M H, Berkson J and Haines E F. The urinary excretion of radioiodine in various thyroid states. *J Clin Investigation* 26 1133 1151)

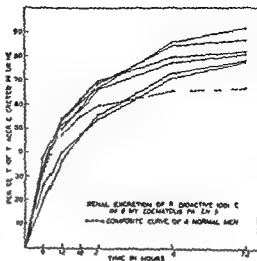


FIG 118 THIOCYANATE GOITER Histologic section showing marked hyperplasia. Myxedema may occur with such goiters (Ranson R R and McArthur J W. Radio iodine its use as a tool in the study of thyroid physiology. *J Clin Endocrinol* 7 235 263)



FIG 119 THIOCYANATE GOITER The same wild hyperplasia is to be seen (Ranson R R and McArthur J W. Radio iodine its use as a tool in the study of thyroid physiology. *J Clin Endocrinol* 7 235 263)



FIG 117 EFFECT OF THYROTROPIC HORMONE Effect of thyrotropic hormone on rat thyroid as well as demonstration of freezing drying fixation technic on histology of the thyroid (A) Rat thyroid Photomicrograph of section prepared by the usual methods of fixation Bunsley stain (B) The same but prepared by the freezing drying technic Note absence of vacuolization which de Robertis believes is an artefact (C) The same 3 hrs after injection of TSH Note increase in particles in thyroid cells bulging of cell apices toward colloid increased height of cells and enlargement of capillaries at cell bases Resorption of colloid underway (D) The same after 10 days of daily injections of TSH Note further increase in height of cells diminishing size of colloid reservoirs increase in number as well as size of capillaries (de Robertis E Cytological and cytochemical bases of thyroid function Tr New York Acad Sc 50 31/ 335)

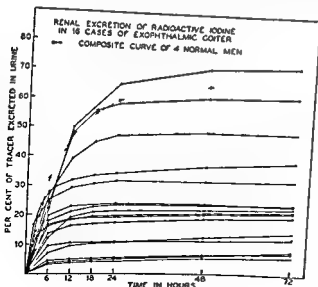


CHART 28 (Left) URINARY EXCRETION OF RADIOIODINE IN EXOPHTHALMIC GOITER Each case (total 16) varied in severity of the disease and amount of urinary radioiodine After an initial period of rapid excretion of radioiodine there is a constant slow output For comparison the composite curve of normal men is illustrated (Keating F R Power M H Berkson J and Haines S F The urinary excretion of radioiodine in various thyroid states J Clin Investigation 26 1138 1151)

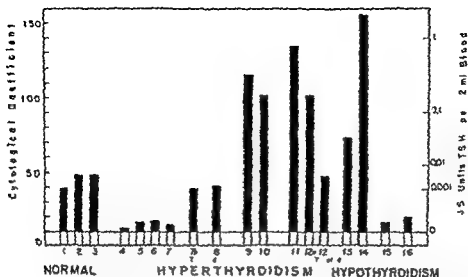


CHART 30 PITUITARY THYROID STIMULATING HORMONE (TSH) IN BLOOD OF PATIENTS WITH DIFFERENT TYPES OF THYROID DISEASE. Diagram indicating assay of thyroid stimulating hormone (TSH) in 16 human cases. On the left side cytologic coefficient (C_c) of the guinea pig thyroid (i.e. number of colloid droplets per follicle in guinea pig thyroid injected with 2 cc. of blood extract) and on the right side the corresponding concentrations of TSH (in Junkmann Schoeller units) are shown.

CASES	
1 2 3	Normal
4 5 6 7a	Untreated Graves's disease
7b	Same as 7a but after thyroidectomy
8	Graves's disease treated with thiouracil
9	Recurrent toxic goiter with severe proptosis and myxedema of the legs
10	Toxic goiter with localized edema
11 12a	Toxic goiter of the ophthalmic type
12b	Same as 12a but after treatment with thyroid
13	Spontaneous myxedema
14	Postradiotherapeutic myxedema
15	Cretinism intensely treated with thyroid
16	Pituitary myxedema

(de Robertis E. Assay of thyrotropic hormone. J Clin Endocrinol 8:836-956)

FIG 122 TRACHEAL COMPRESSION. How stridor may be produced by bending head and neck laterally when intrathoracic goiter is present.

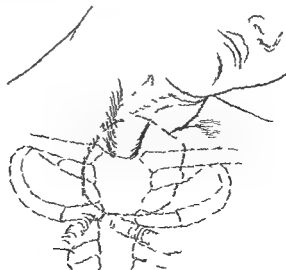




FIG 120 THYROID HYPERPLASIA IN GRAVES'S DISEASE (Left) Photomicrograph showing columnar epithelium in moderately active gland de Robertis considers the vacuolization an artefact i.e. not representing actual spherical entities but he admits that the occurrence of these from ordinary methods of fixation may result from a difference in the peripheral colloid as compared with the central colloid Therefore the vacuolization may represent activity as shown above in the camera lucida drawings (x110) (Right) Photomicrograph of early iodine effect Note cuboidal epithelium lining most alveoli (x110) (For marked involution from iodine see Fig 198 right p 480)

FIG 121 STEPS IN EXAMINATION OF THYROID GLAND (1) Position of thyroid cartilage Laryngeal prominence (Adam's apple) should be centered in plumb line through middle of face downward (2) Head turned to side (3) Thumb on thyroid cartilage displaces it to opposite side (4) Index or middle finger is behind sternocleidomastoid muscle and with thyroid cartilage displaced lobe of thyroid may be palpated if in normal position (5) The subject then swallows the examining fingers are held lightly over the area A low lying or partial sub-sternal lobe (enlarged) will rise on swallowing and may be held up if thumb and finger can be pressed underneath On release the lobe may be palpated as it descends



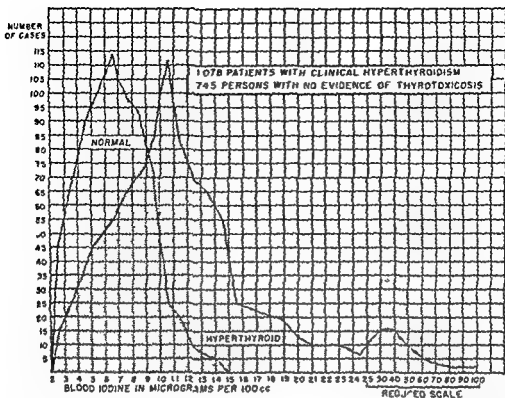


CHART 33. TOTAL BLOOD IODINE. Total blood iodine values in individuals with and without clinical hyperthyroidism. Note the overlapping. Organic or protein bound iodine should not show such wide variations because it is not easily influenced by dietary iodine (Lahey F H and Perkin H J. The level of iodine in the blood. Arch Int Med 65: 887-893).

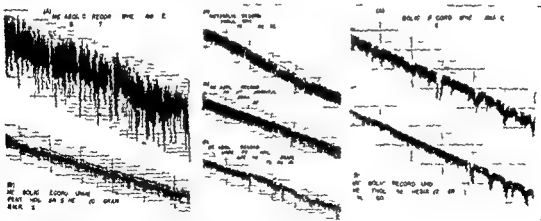


CHART 34. BASAL METABOLIC TEST RECORDS showing effect of pentothal in nervous and hyperthyroid patients

(Left) Nervous patient (A) Awake—BMR plus 31% (B) A sleep with pentothal anesthesia 10.6 Gm—BMR plus 1% (Center) Nervous patient (A) Test performed as outpatient—BMR plus 32% (B) Test performed as inpatient—BMR plus 1% (C) Test performed under pentothal anesthesia (0.6 Gm)—BMR minus 10% (Right) Hyperthyroid patient (severe) (A) Awake—BMR plus 62% (B) Asleep with pentothal anesthesia (2.0 Gm)—BMR plus 60% (Bartels E C. Basal metabolism under pentothal anesthesia. J Clin Endocrinol 9: 1190-1201)

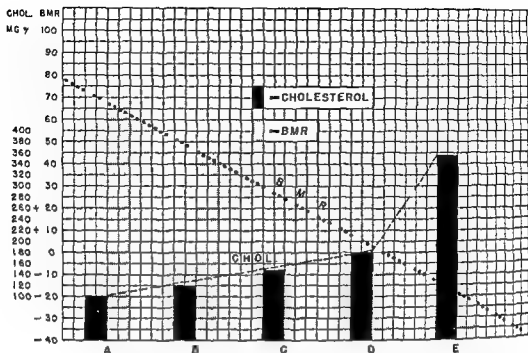


CHART 31 CHOLESTEROL Relationship between average plasma cholesterol values and average basal metabolic rates in various thyroid states (A) Severe hyperthyroidism in crisis or on verge of crisis (B) Hyperthyroidism—average of all types (C) Hyperthyroidism with adenomatous goiter (D) Normal individuals (E) Myxedema Note: The sharp rise in plasma cholesterol is of more value in the diagnosis of myxedema than in hyperthyroidism

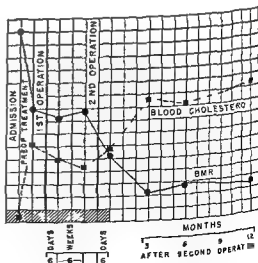
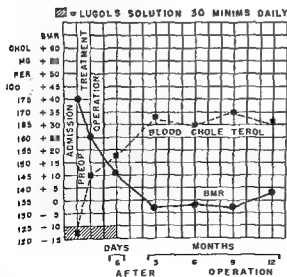


CHART 32 HYPERTHYROIDISM AND PLASMA CHOLESTEROL Averages of plasma cholesterol values and basal metabolic rates before and after subtotal thyroidectomy. Note result of hemi thyroidectomy as compared with subtotal thyroidectomy in one stage (Hurthall L M Blood cholesterol in thyroid disease II Effect of treatment Arch Int Med. 52 86 95)

- b Thyroid cell (or follicle) proliferation (overactivity and multiplication)
- c Deficiency of thyroid cell iodine
- d Reduced or absent hormone synthesis
- e Hyperplastic hyposecretory goiter

C SECOND STAGE—COLLOID STORAGE

- 1 First stage should lead to thyroid deficiency as occurs in thioracil administration but it is assumed that variable conditions exist as
 - a Effective concentration of hypothetical goitrogens
 - b Bodily demands for thyroid hormone
 - c Availability of iodine in physiologic or pharmacologic amounts
- 2 Periodical absorption of iodine at abnormal rate by hyperplastic thyroid cells
 - a Absorption of iodine and colloid storage is faster than conversion of colloid to hormone because of decreased proteolytic enzymes
 - b Colloid is stored i.e. colloid goiter

D THIRD STAGE—COLLOID NODULES

- 1 Irregular follicular development is aided by budding in hyperplastic stage
- 2 Another period of iodine unavailability or increased goitrogen activity is assumed
- 3 Hormone synthesis is decreased
- 4 Hyperplasia and new follicle formation occur while colloid is being slowly absorbed from the others
 - a Hormone synthesis is increased and thyrotropic hormone is suppressed causing a change in polarity
 - b Again with change in polarity by variation of conditions colloid is deposited in new or partially depleted follicles
 - c Larger acini
 - (1) Pressure is proportional to number of active cells secreting colloid
 - (2) Colloid is thus trapped more effectively
 - (3) Thyroid epithelium becomes
 - (a) Flattened
 - (b) Atrophic
 - (4) Mechanism is possibly similar to any secreting cyst

- d Atrophic epithelium surrounding colloid stimulates fibrous tissue proliferation resulting in a colloid nodular goiter

E FOURTH STAGE—Development of thyroid deficiency or excess in colloid nodular goiter can be postulated by variation of conditions which permit (see Fig 123)

- 1 Crowding out of all responsive thyroid tissue
- 2 Continuous stimulation of responsive thyroid cells to hyperthyroidism by above mechanism
 - a Within hypersecretory nodules
 - b Superimposed upon a hyperplastic goiter

III RELATION TO CRETINISM (see 24 IV, VI)

A THYROID FUNCTION

- 1 Prenatal
 - a Fetus with goiter may be stillborn
 - b Infant with goiter (large) with euthyroidism
 - c Deficiency may appear soon postnatally or much later
- 2 Postnatal—in children with goiter
 - a Responsive thyroid tissue present
 - b Less marked abnormalities than with thyro aplasia

B CHARACTERISTICS^{13, 14}

- 1 Same as in other cretins
- 2 Deaf mutism
- 3 Feeble mindedness
- 4 Idiocy
- 5 Cerebral diplegia
- 6 Tetany

C OUTCOME OF ENDEMIC CRETIN WITH GOITER

- 1 Thyroid function—when unchanged
 - a Thyroid deficiency remains
 - b Cretinous appearance maintained
 - c Mental retardation
 - (1) Marked
 - (2) Idiocy may occur depending on degree of thyroid hypofunction
 - d Slight genital development if some thyroid secretion is present
- 2 Thyroid function increasing to normal during
 - a Childhood
 - (1) Cretinous appearance may be lost

SECTION 15

ENDEMIC GOITER

I ETIOLOGY

A GENERAL INFLUENCES

- 1 Heredity—by increased susceptibility to goitrogenic factors^{10 40 47 53 56}
- 2 Geographic^{41 43 61 67}

a These are considered to be due to low iodine content of water and/or soil

b Endemic cretins are found in the following areas

- (1) Pyrenees
- (2) Central Alps
- (3) Himalayas
- (4) Carpathian Mountains
- (5) Certain mountainous sections of Germany
- (6) Parts of Persia
- (7) Northwestern districts bordering Pacific Ocean (United States and Canada)
- (8) Valleys of Sudan
- (9) Northern Italy
- (10) England
- (11) Russia
- (12) Finland
- (13) Great Lakes
- (14) White Mountains of New Hampshire
- (15) Philippines⁴⁰

c Endemic goiter is rare in Japan⁴⁷

3 Infection—on account of unsanitary conditions^{15 41 43 44 60}

4 Goitrogenic factors—known or unknown^{3 7 9 14 17 21 23 33 35-37 44 48 50 54 57 9}

a The following produce experimental goiter but have not been proved either singly or in combination, as the cause in humans

b Dietary deficiencies or abnormalities⁴⁴

- (1) Deficiency of
 - (a) Iodine
 - (b) Vitamins A B or C
- (2) Excess of
 - (a) Fat
 - (b) Fatty acids
 - (c) Lime^{30 36}
 - (d) Proteins (as meat)

(3) The following foods may be factors⁹

- (a) Bran
- (b) Cabbage³⁸
- (c) Ground nuts
- (d) Maize
- (e) Brassica seeds
- (f) Turnips¹⁷
- (g) Rutabagas¹⁷

c Agents

- (1) Thiourea derivatives^{14 15 26 47 51}
- (2) Phenyl thiocarbamide¹
- (3) Sulfamylguanidine³
- (4) Cyanates⁴⁴
- (5) Cyanides^{1 11}
- (6) Promizole³³

5 Combination of any or all above especially during times of increased demands of²³

- a Puberty
- b Pregnancy¹⁰
- c Menopause
- d Cold¹¹

II HYPOTHETICAL MECHANISM OF DEVELOPMENT OF ENDEMIC GOITER^{34 9}

A PREMISE—Inadequate iodine metabolism or hormone synthesis

- 1 Iodine deficient water or food supply
- 2 Malabsorption of iodine by
 - a Gastro intestinal tract
 - b Thyroid gland from effect of goitrogens
- 3 Insufficient thyroid hormone synthesis due to goitrogens

B FIRST STAGE—HYPERPLASIA^{6 11 24 40}

- 1 Thyrotropic hormone production is increased by
 - a Iodine deficiency acting on pituitary cells
 - b Goitrogen
 - (1) Depriving thyroid of iodine
 - (2) Blocking thyroid hormone synthesis

2 Results

- a Thyroid cell hyperplasia (overactivity)

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- (2) Growth at normal rate
- (3) Normal puberty and reproductive

b Adulthood

- (1) Cretinous appearance retained

- (2) Growth absent or slightly below normal

- (3) Sexual function improves

- 3 Hyperthyroidism may develop plus findings as noted above

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SECTION 16

COLLOID GOITER

SYNONYMS

Adolescent	Simple
Early endemic	Sporadic
Iodine deficiency disease	

I DEFINITION

Uniform and variable enlargement of the thyroid gland due to an excessive colloid accumulation without gross nodular formation

II APPEARANCE

Normal except for goiter and unless hypothyroidism is also present (see 24 II Fig 124)

III AGE

In endemic areas goiter appears early in life and lasts longer majority occur about the time of puberty and diminish in size after a few years

IV SEX

Majority in females

V MENTAL DEVIATIONS

None except possibly with hypothyroidism (see 24 V 25 V)

VI PHYSICAL STATUS

A THYROID

Enlargement may be variable uniform symmetrical or asymmetrical less firm than hyperplastic gland no bruit or thrill

B In toto

Normal, except with hypothyroidism (see 24 VI, 25 VI)

VII LABORATORY DATA

Normal findings except if associated hypothyroidism is present (see 24 VII 25 VII)

VIII ETIOLOGY—see 15 I

IX PATHOLOGY

A GROSS—THYROID

- 1 Enlarged
- 2 Nonvascular
- 3 Soft
- 4 Cross section
 - a Pale
 - b Honeycombed
 - c Surface is divided imperfectly by fibrous septa

B MICROSCOPIC—THYROID

- 1 Follicles
 - a Size
 - (1) Variable
 - (2) Dilated usually

b Colloid

- (1) Large amounts
- (2) Thick
- (3) Stains readily
- (4) Iodine content decreased

2 Cells

- a Flat
- b Cuboidal occasionally
- c Hyperplastic areas may be found

3 Stroma

- a Amount decreased
- b Fibrous bands are present
- c Lymphocytic collections
- d Hyaline degeneration

4 Glandular vascularity

- a Decreased

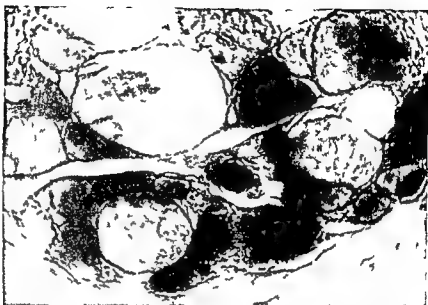


FIG 123 RADIOACTIVE IODINE IN NORMAL THYROID GLAND Normal thyroid gland showing variation in amount of radioactivity (dark areas) from follicle to follicle (x 160) This evidence supports the thesis of formation of colloid or endemic goiter as outlined herein (Fitzgerald P J and Foote F W Jr The function of various types of thyroid carcinoma as revealed by the radioautographic demonstration of radioactive iodine J Clin Endocrinol 9 1153 1170)

(2) Administration of 250 gammas of iodine per day to:

(a) Children

(b) Pregnant women

2 Desiccated thyroid—indications

a Hypothyroidism may be corrected

b Pregnant women to ensure adequate hormone supply

c Gland may shrink but this is unlikely unless accompanied by thyroid deficiency

3 Thyroid enlargement may subside with out therapy

B SURGICAL—When the goiter is large and without thyroid deficiency then subtotal thyroidectomy may be justified because of

1 Cosmetic reasons

2 Substernal extension

3 Tracheal pressure

XV PROGNOSIS

1 GENERAL

1 Little is known about outcome

2 Dependent on complications

3 General health usually good

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FIG 174 COLLOID GOITER Patient with a colloid goiter before and after operation
No substernal extension Removed for cosmetic reasons

- b Increased—sometimes forming non toxic vascular diffuse colloid goiter
- 5 Changes that may develop

- a Cyst formation

- (1) True cyst is of follicular origin
 - (a) Size—may be enormous
 - (b) Monolocular or multilocular
 - (c) Fluid is
 - [1] Serous
 - [2] Chocolate brown
 - (d) Cholesterol crystals may be formed
 - (e) Walls are
 - [1] Thin
 - [2] Thick

- (2) False cyst is caused by a hemorrhage which becomes

- (a) Necrotic
- (b) Encapsulated
- (c) Absorbed

- (3) Arteries and veins may increase
- b Hyperplasia with or without hyperfunction

- c Malignant degeneration

- d Colloid adenoma

C TYPES OF GOITER

1 Congenital

- a Simple parenchymatous

- (1) Colloid practically absent
- (2) Large strands of cuboidal cells with abnormally large nuclei
- (3) Embryonic hyperplasia probably

- b Telangiectatic—hyperplasia of

- (1) Large cavernous blood vessel
- (2) Epithelium

- c Colloid

- (1) Typical colloid gland
- (2) Result of iodine effect on previous hyperplasia during fetal life

2 Colloid

- a Occurrence

- (1) Children
- (2) Young adults

- b As above (1a) with euthyroidism few follicles with dark staining partly absorbed colloid

- c Large follicular type with epithelium which is

- (1) Pale, small
- (2) Cylindrical, arranged in cushion like projections

d Small follicular

- (1) Small acini amidst many epithelial cells
- (2) Some undifferentiated or with hyperplasia

X SYMPTOMATOLOGY

A GENERALLY NONE

B HYPOTHYROIDISM—Varying degrees of hypofunction may be found (see 24 \II, 25 \II)

XI DIAGNOSIS

A PHYSICAL STATUS

- 1 Normal except for a uniform or variable enlarged thyroid gland
- 2 Hypothyroidism (see 24 \IV, 25 \IV)

B LABORATORY DATA—All normal

XII DIFFERENTIAL DIAGNOSIS

—see 35 \I, \II

XIII COMPLICATIONS SEQUELAE AND ASSOCIATED DISEASES

A SUMMARY

- 1 Cyst formation causes pressure if it is very large
- 2 Cretins may develop in severe endemic areas
- 3 Hypothyroidism in different degrees
- 4 Malignant degeneration
- 5 Colloid adenomatous goiter
- 6 Hyperthyroidism

XIV TREATMENT

A MEDICAL

1 Prophylaxis

- a In endemic areas prophylactic (pharmacologic) use of iodine has reduced the incidence of simple goiter

b Results differ depending on

- (1) Locality
- (2) Institution of control measures

c Iodine may be derived from

- (1) Dietary program
 - (a) Sea foods
 - (b) Leafy vegetables
 - (c) Iodized salt
 - (d) Balanced intake

- 3 Diffuse and nodular
 - a Diffuse colloid plus nodular parenchymatous
 - b Diffuse colloid plus nodular colloid
 - Diffuse parenchymatous plus nodular parenchymatous
 - d Diffuse parenchymatous plus nodular colloid
- 4 Malignant degeneration—rare (see 35 \B)

VIII SYMPTOMATOLOGY

A GENERAL COMPLAINTS

- 1 None
- 2 Mechanical from tracheal compression
 - a Cough
 - b Dyspnea
 - c Stridor
 - d Dysphagia rarely⁶

B HYPOTHYROIDISM (see 24 \II 25 \II)

C HYPERTHYROIDISM (see 26 \II)

IX DIAGNOSIS

A PHYSICAL STATUS

- 1 Normal, except for findings in thyroid gland
- 2 Signs of
 - a Hypothyroidism
 - b Hyperthyroidism

X DIFFERENTIAL DIAGNOSIS—see 35 \I, \II

XI COMPLICATIONS SEQUELAE AND ASSOCIATED DISEASES

A HEMORRHAGE—Often sudden and alarming

B PRESSURE SYMPTOMS

C HYPOTHYROIDISM

D HYPERTHYROIDISM

F MALIGNANCY—From 0.5 to 17.1 per cent of all reported nodular goiters¹⁻⁷ ■

F RECURRENT NODULAR GOITER

- 1 After removal of nodular nontoxic goiter recurrence is probable in due time
- 2 Greater resection may prevent this

G DEGENERATIVE CHANGES (see 2 \A 2, 4 17 VIII B 3)

XII TREATMENT

A SURGICAL

1 Indications

- a Pressure symptoms
- b Hemorrhage
- c Malignant degeneration 3 5 8 9

2 Results

- a Recurrence may slowly develop in the majority depending on
 - (1) Amount of thyroid tissue ■■ moved
 - (2) Time elapsed postoperatively
- Regrowth occurs in variable degrees rarely with hyperthyroidism
- c Myxedema may develop

■ COMPLICATIONS

- 1 Myxedema
- 2 Hyperthyroidism

XIII PROGNOSIS

A WITHOUT TREATMENT

- 1 Normal, except for enlarged thyroid gland
- 2 Complications may develop at any time (see above)

B SURGICAL—see above

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SECTION 17

NODULAR (MULTIPLE) GOITER

SYNONYMS

Nontoxic nodular goiter
Nontoxic adenoma

Multiple adenomatous goiter
Colloid adenoma

I DEFINITION

Any goiter containing multiple palpable nodules is included in this group. Single nodules are discussed under tumors of the thyroid (see 35 VI VII). At operation the latter may be a large colloid nodule in a colloid goiter with numerous smaller nodules which are not palpable.

II APPEARANCE

Normal, except goiter may be quite prominent

III AGE

After 30 years

IV PHYSICAL STATUS

A THYROID

Size variable, nodules may be small or large, soft or firm, smooth or irregular, may displace thyroid cartilage laterally, may become pendulous, enlarged neck veins in some (see Figs 125 and 126)

B IN toto

Normal

V LABORATORY DATA

Normal

VI ETIOLOGY—see 15 I

VII PATHOLOGY

A GROSS—THYROID

- 1 Enlargement to all degrees
- 2 Nodules are
 - a Different in
 - (1) Size
 - (2) Shape
 - b Scattered throughout the gland which has an abundance of parenchymatous tissue
- 3 Stroma
 - a Amount variable
 - b Fibrous
 - c Calcareous deposits may occur
- 4 Cross section shows encapsulated or bulging nodules with interlaced fibrous tissues
- 5 Vascular in some

B MICROSCOPIC—THYROID

- 1 Nodules
 - a Acini
 - (1) Sizes differ
 - (2) Compression near the nodules due to pressure
 - b Epithelium—flat
 - c Colloid—variable amounts
- 2 Fetal adenoma—see 35 IX A 2 b

3 Changes that may develop

- a Degeneration
 - (1) Amyloid
 - (2) Fatty
 - (3) Mucoid
 - (4) Hyaline in
 - (a) Stroma
 - (b) Perivascular areas
- b Hemorrhage into
 - (1) Adenoma
 - (2) Cyst
- c Cavernous angioma
- d Cyst in large follicle
- e Calcification

C TYPES OF GOITER

- 1 Nodular parenchymatous
 - a Large follicle or macrofollicular
 - b Small follicle or microfollicular
 - c Embryonal or trabecular with no apparent follicle formation
 - d Fetal or tubular—follicles like tubules lined with epithelium which is
 - (1) Cuboidal
 - (2) Cylindrical
- 2 Nodular colloid
 - a Papillary large follicle
 - b Simple adenoma

SECTION 18

INTRATHORACIC GOITER

I DEFINITION

The term intrathoracic goiter indicates an adenomatous or nodular goiter which for the most part, is entirely within the thorax. Substernal goiter indicates a goiter which has partially descended through the superior straight behind the sternum.

II APPEARANCE

Normal, occasionally swelling of face and with or without cyanosis.

III AGE

Congenital rarely; average age about 40 years.

IV SEX

Greater incidence in males.

V PHYSICAL STATUS

A THYROID

Absent thyroid tissue in neck, inability to palpate bottom of lower poles on swallowing; goiter may appear to be entirely in neck but have large intrathoracic extension.

B OTHER SIGNS

1 Venous distention

May be huge in neck (frog-neck appearance), chest (infra-red photography can easily demonstrate venous changes); upper abdomen (see Figs 127, 130 and 136).

2 Larynx

May be fixed.

3 Tracheal cartilage

Displacement may be palpated.

4 Demonstration of stridor

May be heard in any position which increases tracheal compression: head is held forward, backward or turned to either side.

5 Sternum

Dullness over it on percussion, if goiter is sufficiently enlarged.

6 Color

Cyanosis rarely.

VI ROENTGENOLOGIC FINDINGS

A MISCELLANEOUS (see Figs 131, 133, 135 and 137)

1 Chest

Intrathoracic tumor is evident; goiter may reach aortic arch rarely lower.

2 Trachea

Deviation illustrated by Bucky films taken in antero-posterior, oblique, lateral positions.

VII ETIOLOGY

A ENDEMIC GOITER (see 15 I)

B INTRATHORACIC DESCENT OF GOITER

1 Mechanism (see Figs 128 and 129)

a A goiter must be of considerable size before there is a tendency to descend.

b Normal or hyperplastic glands are not apt to leave their position.

c Weight of gland as well as size subject it to pressure traction from muscles of swallowing.

d Direction of least resistance is downward through superior straight of thoracic cage.

ward through superior straight of thoracic cage.

e Blood supply is carried along with the descending gland.

2 Goiter may become fixed if it

a Enlarges sufficiently.

b Cannot pass completely through the thoracic straight; lower portion may become anchored while the upper part is too large to follow downward.

c Extends behind the trachea.

C ABERRANT THYROID TISSUE (see Fig 134)[†]

1 Extremely rare.

2 Origin from embryonic cell rests.



FIG 125 NODULAR GOITER (*Left and center*) Age 41 female Large nodular goiter with slight substernal extension (*Right*) After removal



FIG 126 NODULAR GOITER BECOMING PENDULOUS

D MALIGNANT TUMOR OF LUNG

- 1 Hemoptysis
- 2 Cough is more frequent
- 3 Chest roentgenogram
 - a Mediastinal shadow may be displaced to opposite side
 - b Pleural effusion
- 4 Diagnosis may be established by
 - a Bronchoscopy
 - b Biopsy
 - c Analyses of pleural fluid for malignant cells

XII COMPLICATIONS SEQUELAE AND ASSOCIATED DISEASES**A SUMMARY**

- 1 Severe suffocating spells
- 2 Hemorrhage (sudden)
- 3 Circulatory embarrassment (rare)
- 4 Malignant degeneration (uncommon)
- 5 Acute infections

XIII TREATMENT**A SURGICAL**

- 1 Comment
 - a Oxygen or oxygen and helium for stridor
 - b Intratracheal intubation by anesthesiologist if necessary
 - c Removal of goiter in all cases if expedient
- 2 Operative procedure^{1 3 4}
 - a Intratracheal cyclopropane oxygen anesthesia
 - b Curved collar incision dividing platysma
 - c Raise upper flap above notch of thyroid cartilage
 - d Free sternocleidomastoid muscle on each side
 - e Bilateral high division of prethyroid muscles
 - f Ligation and division of superior thyroid vessels
 - g Division of isthmus and exposure of the trachea
 - h Ligation and division of middle thyroid veins
 - i Exposure of recurrent nerve inferior parathyroid and inferior thyroid artery if feasible at this stage

- j If not, apply traction to upper pole of the lobe and insert finger into chest behind goiter
- k Deliver intrathoracic goiter by combined upper pull and inferior pressure, decreasing transverse diameter of goiter, entering thoracic strait
- l If delivery is not accomplished
 - (1) Enter lobe in neck
 - (2) Break up and evacuate part of central portion of intrathoracic goiter
- m Deliver intrathoracic goiter now reduced in size
 - (1) Avoid injury to apical pleura
 - (2) Place moist gauze pack in thoracic space
- n Ligate inferior thyroid artery, if not already done, in continuity
- o Expose
 - (1) Recurrent laryngeal nerve in neck
 - (2) Inferior parathyroid
- p Subtotal resection of thyroid lobe including all of intrathoracic portion
- q Reconstruct remnant to trachea
- r Inspect other lobe and if indicated do subtotal resection particularly if low in position
- s Gauze pack in intrathoracic space
- t Suture prethyroid muscles
- u Close platysma and skin with clips
- v Inspect larynx and clear trachea of secretions with intratracheal catheter or bronchoscope

- 3 Postoperative complications (see Fig 138)
 - a Intrathoracic accumulation of serum
 - b Hemorrhage
 - c Infection of
 - (1) Wound
 - (2) Intrathoracic space
 - d Pulmonary infection
 - e Atelectasis

XIV PROGNOSIS**A GENERAL**

- 1 Complications may occur suddenly
- 2 Surgery can relieve
 - a Symptoms
 - b Signs

VIII PATHOLOGY

A GROSS—see 16 VII A

B MICROSCOPIC—see 16 VII B

IX SYMPTOMATOLOGY

A HORMONAL—Thyroid function may be

- 1 Normal
- 2 Decreased
- 3 Increased

B COMPRESSION OF

- 1 Trachea
 - a Cough
 - (1) Occasionally
 - (2) Local tracheitis may cause it
 - b Paroxysmal stridor and dyspnea are due to
 - (1) Mucus in compressed portion
 - (2) Flexion of head producing increased obstruction
 - (3) Hemorrhage into adenoma
 - c Constant stridor and dyspnea are caused by
 - (1) Very narrow passage through blocked area
 - (2) Sudden increased pressure from above mentioned causes
- 2 Neck veins
 - a Sensation of congestion in the head
 - b Giddiness, especially on leaning over

C PRESSURE ON

- 1 Esophagus
 - a Extremely infrequent
 - b When dysphagia is present consider
 - (1) Malignant invasion
 - (2) Plummer Vinson syndrome (atrophy of esophageal mucous membranes or esophageal webs)
- 2 Laryngeal nerves
 - a Uncommon
 - b Malignant extension usual cause

X DIAGNOSIS

A SYMPTOMATOLOGY (see above) — Complaints from compression of

- 1 Trachea
- 2 Neck veins

B SIGNS

- 1 Thyroid tissue is absent in neck
- 2 Venous distention in
 - a Neck
 - b Abdomen
- 3 Stridor may be demonstrated

C ROENTGENOGRAMS

- 1 Intrathoracic tumor
- 2 Tracheal cartilage is often displaced

XI DIFFERENTIAL DIAGNOSIS

A ANEURYSM

- 1 Variable degrees of compression and displacement which may involve
 - a Trachea
 - b Mediastinum
 - c Vertebrae
- 2 Pulsations are expansile under fluoroscopy examination, but unreliable because not always evident
- 3 Tracheal tug may be found
- 4 Heart examination
 - a Loud, ringing aortic second sound
 - b Harsh, high pitched systolic murmur over aneurysm
 - c Diastolic murmur may also be heard if
 - (1) Aortic ring is dilated
 - (2) Disease of aortic valves is present

5 Oblique roentgenograms may aid in diagnosis

6 Serologic tests usually positive

B ENLARGED THYMUS GLAND OR THYMIC TUMOR

- 1 Thyroid cartilage is in its normal position
- 2 If located in anterior mediastinum trachea is displaced laterally
- 3 On extension of head in children an enlarged thymus rises on swallowing
- 4 Chest roentgenogram
 - a Thyroid lies lower in chest and over shadows heart (covers auricles)
 - b Shape is triangular, if an enlarged gland is present
 - c Soft and regular outline
- 5 Response to roentgen therapy some times

C LYMPHOMAS (see Fig 137)

- 1 Lymphadenopathy elsewhere in body
- 2 Hematologic abnormalities
- 3 Chest roentgenogram
 - a Thyroid cartilage in normal position
 - b Trachea is not displaced unless predominantly unilateral
 - c Bilateral often
 - d Infiltration may be extensive
- 4 Biopsy of gland
- 5 Response to roentgen therapy often

FIG 130 INTRATHORACIC NODULAR GOITER
Age 55 female Hyperthyroidism and recurrent adenomatous goiter intrathoracic Infra red photograph Adenomatous left lobe removed for hyperthyroidism Weight 128 lbs Pulse 80 BMR 1 year later—minus 1% Returned 13 years later with recurrent goiter and symptoms of mild hyperthyroidism Weight 115 lbs Pulse 86 BMR plus 15% A large intrathoracic goiter extending to ninth rib posteriorly displacing trachea to right and posteriorly Bilateral enlargement at operation almost entirely intrathoracic Most of tumor was removed by marsupialization until remaining mass could be extricated Pathologic diagnosis multiple colloid adenomatous goiter with coincident fetal adenoma Subsequent course uneventful with gain of 20 lbs in 3 months



FIG 131 INTRATHORACIC GOITER Completely intrathoracic goiter (Lahey F H Completely intrathoracic goiter Medico-Surgical Tributes to Harold Brunn Berkeley Univ California Press p 244)

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FIG 127 INTRATHORACIC GOITER SHOWING DILATED VEINS ON UPPER CHEST



FIG 129 EXTRATHORACIC AND INTRATHORACIC NODULAR GOITER Nodular goiter which is lodged in superior strait and also intrathoracic Marked anterior and posterior trachea compression (Lahey F H and Swinton N W Intrathoracic goiter *Surg Gynec & Obst* 59 627 637)



FIG 128 NODULAR GOITER Drawing of nodular goiter with retrotracheal and substernal extension Clinically this would appear to be entirely in the normal thyroid position

FIG 135 INTRATHORACIC NODULAR GOITER. Deviated trachea from nodular goiter partially substernal. Marked narrowing and displacement due to partly intrathoracic goiter. The position of the goiter renders it a fulcrum upon which the trachea may be compressed farther on bending head and neck laterally. This may occur during sleep, causing dyspnea, particularly during an acute upper respiratory infection when mucous may clog the narrowed airway.



FIG 136 INTRATHORACIC NODULAR GOITER WITH DILATED UPPER ABDOMINAL VEINS. Dilated veins due to superior vena cava compression.



FIG 132 PARATRACHEAL GOITER Para tracheal goiter with substernal extension and tracheal deviation (Lahey, F H Completely intrathoracic goiter Medico Surgical Tributes to Harold Brunn Berkeley Univ California Press p 248)



FIG 133 INTRATHORACIC GOITER Intrathoracic goiter with portion above clavicle Note marked tracheal compression Oblique view showing forward displacement and compression of trachea from retrosternal extension of goiter



FIG 134 ABERRANT INTRATHORACIC GOITER Patient had an adenoma of the thy

roid removed It was substernal in the midline and about the size of an orange A bilateral subtotal thyroidectomy was done the right lobe did not have any adenomatous changes Eleven years later a chest plate taken as a routine procedure showed a mass on the right side Patient had no symptoms except moderate dyspnea The tumor was not considered to be of thyroid origin A thoracotomy and excision of the large smooth encapsulated goiter was performed It was about 10 x 15 x 10 cm in size and was situated above the hilum of the right lung in the mediastinum between the azygos vein and the superior vena cava The goiter had no connection with the neck and probably was derived from an aberrant thyroid Patient survived



FIG 138 INTRATHORACIC NODULAR GOITER (Top left) Intrathoracic goiter (Top right) Specimen removed (15 cm long) (Bottom) Chest roentgenogram showing extent of cavity from which goiter was removed. Space packed with gauze.





FIG 13/ INTRATHORACIC GOITER SIMULATING LAMPHOMATOUS TYPE OF TUMOR (Left) Age 53 Intrathoracic tumor proved to be an intrathoracic goiter Paralysis of right vocal cord Marked hoarseness venous distention and cough for 3 months No changes with roentgen therapy On operation an adenoma arising from left lower lobe 6 in in diameter was removed without any complications Note tracheal displacement as shown on roentgenogram Cricoid cartilage was in its normal position Laryngeal paralysis remained after operation Pathologic report multiple colloid adenomatous goiter (Right) Condition 4 months after operation Recurrent laryngeal paralysis still present 18 months later

■ Degenerative changes

(1) Abscesses

(2) Gangrene

B MICROSCOPIC—THYROID

1 Acini

a Normal

b Atrophic

c Destruction—suppurative type

2 Stroma

a Swollen

b Leukocytic infiltration

c Fibrous tissue abundant

X SYMPTOMATOLOGY

A GENERAL

1 Pain in anterior neck aggravated by swallowing

2 Thyroid

■ Tenderness

b Visible swelling may be noted

3 Malaise

4 Fever chills rarely

5 Anorexia

6 Nausea

7 Vomiting

8 Shooting pains occasionally in

a Ears

b Occipital region

c Lower jaw

d Shoulders

9 Laryngitis or laryngotracheitis

10 Cough

11 Palpitation

12 Roaring in ears

13 Vertigo

14 Delirium in children

XI DIAGNOSIS

A GENERAL

1 Tenderness and swelling of thyroid gland accompanied by a mild or severe systemic reaction

2 Abscess formation in suppurative thyroiditis

XII DIFFERENTIAL DIAGNOSIS

A TONSILLITIS—Examination of throat may establish the diagnosis

B CERVICAL ADENITIS—Location of glands should identify lesion

C LUDWIG'S ANGINA

1 An acute streptococcal or other infection which

a Starts in the floor of the mouth

b Spreads to jaw and down into neck

2 Tongue is pushed upward because of the swelling and induration in the floor of the mouth

D MALIGNANT GOITER (especially sarcoma)

1 Older age group

2 Surrounding tissue may be involved

XIII COMPLICATIONS

SEQUELAE AND ASSOCIATED DISEASES

A ABSCESS FORMATION

B CELLULITIS

C SEPTICEMIA (infrequent)

D GANGRENE—Rare in nonsuppurative type

E HEMORRHAGE—Occurrence more often in suppurative thyroiditis

F MYXEDEMA (uncommon)

G ASPHYXIA (occasionally in both kinds)

H PERFORATION (once in a while) into

1 Trachea

2 Esophagus

3 Pleura

4 Mediastinal space

XIV TREATMENT

A MEDICAL

1 Trial of

a Sulfonamides

b Penicillin—infection may be resistant

c Thiouracil has been suggested⁴

d Aureomycin, streptomycin and chloromycetin have not been adequately evaluated

2 Local applications

a Early—cold compresses or ice packs

b Later—hot packs

B SURGICAL

1 Intervention at the proper time although it may be difficult to determine

2 Indications

a Abscess formation

b Probable suppuration

(1) Protracted course

(2) Increasing pain

(3) Fever

(4) Leukocytosis

(5) Enlarging gland

3 Procedure

a Incision and drainage

b Lobectomy

SECTION 19

THYROIDITIS ACUTE NONSUPPURATIVE AND SUPPURATIVE

I DEFINITION

- | | |
|------------------------|--|
| A ACUTE NONSUPPURATIVE | An inflammatory process of the thyroid gland without abscess formation |
| B ACUTE SUPPURATIVE | Abscess may occur in normal pre existing, colloid nodule or nonsuppurative thyroiditis |

II APPEARANCE

Not unusual

III AGE

Any, suppurative type more frequent in children, rare from 15 to 60 years

IV SEX

Greater incidence in females

V PHYSICAL STATUS

- | | |
|-----------|---|
| A THYROID | Swollen, tender, overlying skin is hyperemic edematous warm to touch may be very enlarged in suppurative type |
|-----------|---|

II OTHER SIGNS

- | | |
|---------------|--|
| 1 Voice | Hoarseness |
| 2 Temperature | Fever, but never very high |
| 3 Muscles | Flexion of neck causes muscle spasm, abdominal rigidity is rarely found in children painful swallowing |

VI LABORATORY DATA

- | | |
|----------------------|------------------|
| A GENERAL | |
| 1 White blood cells | May be increased |
| 2 Sedimentation rate | May be increased |

VII ROENTGENOGRAPHIC FINDINGS

Marked dislocation of the larynx and trachea if swelling is sufficient

VIII ETIOLOGY¹

A MICRO ORGANISMS²

- 1 Streptococcus
- 2 Staphylococcus
- 3 Pneumococcus
- 4 Bacillus coli
- 5 Bacillus typhosus
- 6 Anaerobic group

- 9 Puerperal infection
- 10 Tonsillitis
- 11 Typhoid
- 12 Pneumonia
- 13 Trauma
- 14 Pyemia

IX PATHOLOGY³

A GROSS—THYROID

- | | |
|-----------------|--|
| B DISEASES | |
| 1 Influenza | |
| 2 Malaria | |
| 3 Smallpox | |
| 4 Measles | |
| 5 Cholera | |
| 6 Dysentery | |
| 7 Mumps | |
| 8 Scarlet fever | |
| | 1 Hard |
| | 2 Friable in some parts |
| | 3 Edematous |
| | 4 Inflammation of capsule may involve surrounding structures |
| | 5 Cross section |
| | a Red surface if late stage of disease mottled white areas |
| | b Fibrous tissue dense |

SECTION 20

CHRONIC NONSPECIFIC THYROIDITIS

I DEFINITION

A subacute or chronic condition of the thyroid gland characterized by various histopathologic changes possibly due to inflammation. It cannot be classified as Riedel's or Hashimoto's struma.

II APPEARANCE

Same as Riedel's or Hashimoto's struma

III AGE

Any

IV SEX

Twenty times more frequent in females

V PHYSICAL STATUS

A THYROID

Variable in contour and firmness, often considered adenomatous goiter or cancer of thyroid, difficult to identify before operation

B IN toto

Normal or findings of hypothyroidism (rare)

VI LABORATORY DATA

Normal except when myxedema is present

VII ETIOLOGY

A UNKNOWN

B MILD INFECTION POSSIBLY

C TRAUMA MAY BE FACTOR

VIII PATHOLOGY¹

A GROSS THYROID—Variable, nothing characteristic

B MICROSCOPIC—THYROID

- 1 Epithelium—absent or mild acidophilia
- 2 Stroma
 - a Fibrosis slight
 - b Round-cell infiltration
 - c Colloid depleted occasionally

IX SYMPTOMATOLOGY

A COMMON

PER CENT

- | | |
|-------------------------------|----|
| 1 Presence of goiter | 25 |
| 2 Enlargement in neck | 25 |
| 3 Pressure sensation | 25 |
| 4 Hoarseness | 8 |
| 5 Dysphagia | 7 |
| 6 Thyroid deficiency symptoms | 6 |

B MISCELLANEOUS

- 1 Nervousness
- 2 Fatigue
- 3 Cough
- 4 Discomfort in neck
- 5 Choking sensation

X DIAGNOSIS

A BIOPSY OF THYROID

- 1 Microscopic studies are necessary for final decision
- 2 Preoperative diagnosis possible in 12 per cent by elimination of other causes of thyroid enlargement

XI DIFFERENTIAL DIAGNOSIS

A HASHIMOTO'S STRUMA (see 22 VI)

- 1 Bilateral
- 2 Nonadherent
- 3 Not hard
- 4 Pressure effects less marked
- 5 Biopsy diagnostic

B RIEDEL'S STRUMA (see 21 VI)

- 1 Unilateral often
- 2 Adherent to surrounding tissues
- 3 Hard
- 4 Pressure changes are more frequent
- 5 Biopsy diagnostic

C NODULAR GOITER (see 17 VI)

- 1 Nodules more discrete
- 2 Nonadherent
- 3 Fewer pressure effects
- 4 Biopsy diagnostic

D INVOLUTED HYPERPLASTIC GLAND

- 1 Previous or associated hyperthyroidism
- 2 Nonadherent
- 3 Pressure effects absent

XV PROGNOSIS

A GENERAL

- 1 Outcome depends on severity of infection

- 2 Inflammation may
 - a Subside rapidly
 - b Develop into abscesses
- 3 Complications may respond to treatment

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SECTION 21

RIEDEL'S STRUMA^{12 14 15}

SYNONYMS

Chronic fibrous type	Ligneous goiter (chronic ligneous thyroiditis)
Woody thyroiditis	Thyroiditis simplex
Iron hard strumitis	Chronic nonsuppurative thyroiditis

✓ I DEFINITION

A specific type of thyroiditis characterized by replacement of normal follicles by dense fibrous connective tissue

II APPEARANCE

Normal individual or may have myxedema (rare)

III AGE

Peak of incidence in fourth decade, range from second to seventh decades

✓ IV SEX

Females and males equally affected according to some, while others report females involved three times as frequently as men ^{8 10}

✓ V PHYSICAL STATUS

A THYROID

- ✓ Enlarges rapidly seldom as large as a goose's egg unit
- ✓ lateral involvement often suggesting focal character
- ✓ bilateral occasionally / very hard / smooth surrounding
- ✓ tissues are invaded causing fixation sometimes painful
- ✓ Normal or findings of hypothyroidism (unusual)

B IN TOTO

✓ VI LABORATORY DATA

Normal except if myxedema is present

✓ VII ROENTGENO

GRAPHIC FINDINGS Trachea may show compression

VIII ETIOLOGY

A UNKNOWN

B THEORIES

- ✓1 Penthyroiditis causes partial constriction of the vessels entering the thyroid gland²
- ✓2 Lesion of inflammatory type due to previous upper respiratory or dental infection

IX PATHOLOGY^{8 12 13}

A CROSS—THYROID

- ✓1 Hard
- ✓2 Fibrous
- ✓3 Cut surface
 - a Dry
 - b White or pinkish white
 - Bloodless
 - d Creaking sound on sectioning
 - Pseudolobulations absent

✓ Extrathyroidal involvement

II MICROSCOPIC—THYROID

- ✓1 Picture of chronic inflammation
- ✓2 Early stage (subacute)
 - a Lymphoid masses are scattered throughout gland
 - b Active fibrosis
 - c Few normal acini
 - d Numerous round cells
 - e No lymph follicles
- ✓3 Late stage (chronic)
 - a Lymphocytes replaced by dense sclerotic tissue
 - b Large keloidlike bundles with few spindle form cells
 - c Small vessels surrounded by round cells
- ✓4 Final stage (healed)—fibrous tissue with few nuclei

E MALIGNANT DISEASE (see 35 \I)

- 1 Pre existing lump in neck
- 2 Growth is rapid
- 3 Adherent
- 4 Firm or hard
- 5 Biopsy diagnostic

F OTHER THYROID DISEASE (see 23)

- 1 Amyloid
 - a Chronic sepsis present elsewhere
 - b Biopsy
- 2 Tuberculosis—biopsy
- 3 Syphilis
 - a Serology positive
 - b Biopsy
 - c Response to treatment

XII COMPLICATIONS SEQUELAE AND ASSOCIATED DISEASES**A TRACHEAL NARROWING (rare)****B MYXEDEMA****XIII TREATMENT****A SURGICAL****1 Indications**

- a Diagnosis
- b Pressure symptoms, if not functional

2 Postoperative complications

- a Tetany is rare
- b Myxedema in 50 per cent

XIV PROGNOSIS**A GENERAL OUTCOME**

- 1 Unknown
- 2 Myxedema in some

REFERENCES

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FIG 139 NONSPECIFIC TYPE OF CHRONIC THYROIDITIS This type does not conform to Riedel's or Hashimoto's thyroiditis. There are beginning scar tissue strands and follicles are disappearing. Inflammatory reaction occurs around the spilled colloid (x 29) (Marshall S F Meissner W A and Smith D C Chronic thyroiditis New England J Med 238 758 766)



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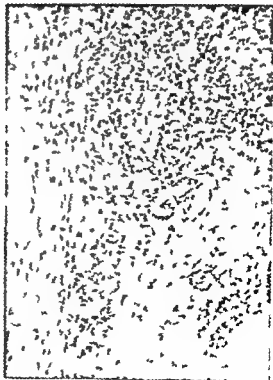


FIG 140 RIEDEL'S STRUMA Scar tissue makes up most of gland. Few follicular remnants. Numerous round cells and scattered lymphocytes ($\times 100$)

X SYMPTOMATOLOGY

A GENERAL

- ✓1 Sudden enlargement in normal thyroid
- ✓2 Pressure effects on the trachea and the esophagus
 - a Discomfort in neck
 - b Choking sensation
 - c Dysphagia (rare)
 - d Cough
 - e Nocturnal asthma
- 3 Dyspnea is unusual
- 4 Painful sometimes
- 5 Voice may be affected, unilateral vocal cord paralysis occasionally
- 6 Mild hypothyroid complaints in a few cases
- 7 Nervousness
- 8 Fatigue

XI DIAGNOSIS

A GENERAL

- 1 Thyroid is
 - a Very hard (woody)
 - b Smooth
 - c Involved
 - (1) In toto
 - (2) Unilaterally most often
 - d Symmetrical⁸
 - e Normal in outline⁶
- 2 Preoperative diagnosis possible in 56 per cent¹⁰
- 3 Biopsy of gland

XII DIFFERENTIAL DIAGNOSIS

A HASHIMOTO'S STRUMA (see 22 \I)

- 1 Thyroid is not as hard as in Riedel's struma
- 2 Bilateral involvement
- 3 Not adherent to surrounding tissue
- 4 Nodular surface
- 5 Pressure changes rarely develop
- 6 Females are more often affected
- 7 Occurrence later in life
- 8 Myxedema commoner

B CHRONIC NONSPECIFIC THYROIDITIS—see 20 \

C CARCINOMA (see 35 \I)

- 1 Primary malignancy
- 2 It may be difficult to distinguish clinically
- 3 Biopsy is diagnostic

XIII COMPLICATIONS
SEQUELAE AND ASSOCIATED DISEASES

A TRACHEAL INVOLVEMENT ✓

- 1 Obstruction
- 2 Compression
- 3 Tracheotomy may be necessary

✓B MYXEDEMA—Occurrence in 1 per cent of cases

XIV TREATMENT

✓A SURGICAL⁷

✓1 Procedure

- a Gland is difficult to remove because of adherence to surrounding structures
- b Wedge shaped piece may be excised over trachea to relieve compression

✓2 Postoperative complications

- a Tetany
- b Recurrent nerve injury
- c Edema of trachea, temporary tracheotomy may be required

✓3 Results

- a Recurrence is possible
- b Myxedema

✓B ROENTGEN

- 1 Indication—may be effective only in early stages¹ 16 17
- 2 Radium has been tried¹

XV PROGNOSIS

A GENERAL OUTCOME

- 1 Entire gland may be destroyed if process continues
- 2 Myxedema

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- 6 Lahey F H Thyroiditis its differentiation from malignancy Lahey Clin Bull 3 194 196 (Jan) 1944

- ✓ b Atrophy
- c Hyperplasia occasionally
- d Clumps
- ✓ e Acidophilia marked
- f Nucleus
 - (1) Basal in tall cells
 - (2) Central in flat cells
- g Mitoses absent
- h Mitochondria
 - (1) Absent
 - (2) Few in number
- ✓ f Stroma
 - a Lymphocytic infiltration may destroy acini
 - b Interstitial fibrosis in variable degrees
 - c Colloid rarely spilled
 - d Blood vessels are not affected

X SYMPTOMATOLOGY

A GENERAL

- 1 Complaints chiefly related to pressure (although not marked)
 - a Dyspnea with exertion or rest
 - b Choking sensation
 - c Dysphagia (infrequent)
- 2 Fatigue
- ✓ 3 Weight gain
- ✓ 4 Thyroid gland enlarges gradually
- ✓ 5 Hypothyroidism
- ✓ 6 Hyperthyroidism may be found in early stages
- 7 Duration of complaints¹³
 - a Average—5 years
 - b Range—9 months to 25 years

XI DIAGNOSIS

A GENERAL

- 1 Occurrence—females usually over 40 years
- 2 Symptomatology
 - a None, except that of mild pressure sometimes
 - b Myxedema occasionally
 - c Differentiate from globus hystericus
- 3 Thyroid gland should be
 - a Symmetrically enlarged
 - b Moderately hard
 - c Freely movable
 - d Nonpainful
 - e Nontender
 - f Biopsied
- 4 Preoperative confirmation is possible in 17 per cent or more

XII DIFFERENTIAL DIAGNOSIS

A RIEDEL'S STRUMA—see 21 \I

B NONSPECIFIC THYROIDITIS (see 20 \I)

- 1 Absence of specific features of other forms of thyroiditis
- 2 History of acute thyroiditis (occasionally)
- 3 Biopsy

C MALIGNANCY (see 35 \I)

- 1 Occurrence in older age group usually
- 2 Surrounding tissues may be involved
- 3 All parts of thyroid are not affected
- 4 Often diagnosis may be dependent on gross and/or microscopic examination of tissue

XIII COMPLICATIONS SEQUELAE AND ASSOCIATED DISEASES

✓ A MYXEDEMA

- 1 Development gradual
- 2 Present in 8 per cent

✓ B TRACHEAL PRESSURE—Rarely of great clinical importance i.e., requiring tracheotomy

XIV TREATMENT

A SURGICAL

- 1 Indications
 - a Pressure symptoms if sufficient, justify removal of isthmus
 - b If malignancy is suspected
- 2 Postoperative complications (unusual)
 - a Hoarseness may persist for months
 - b Injury to
 - (1) Recurrent nerve
 - (2) Parathyroids
- 3 Results
 - a Recurrence is uncommon
 - b Myxedema

B MEDICAL—Thyroid deficiency (see 25 \VI)

✓ C ROENTGEN OR RADIUM^{14 15}

- 1 Some recommend it
- 2 Gland must be biopsied first
- 3 Results have been good

XV PROGNOSIS

A PROGRESSIVE DISEASE

- 1 Process gradually can destroy entire gland causing hypothyroidism
- 2 Malignant degeneration does not follow¹
- 3 Myxedema

SECTION 22

HASHIMOTO'S STRUMA¹

SYNONYMS

Chronic lymphoid type
Struma lymphomatosa

Lymphadenitis (Joll)
Lymphadenoid goiter

✓ I DEFINITION

A specific type of thyroiditis which is characterized by lymphatic infiltration of the parenchyma and eventually by fibrosis

II APPEARANCE

Normal individual except for ✓ enlargement of thyroid gland ✓ hypothyroidism occasionally, and hyperthyroidism rarely

III AGE

Peak of incidence in ✓ fifth decade but may occur from second to seventh decades^{1 7 10}

IV SEX

✓ Females predominate uncommon in males^{1 10 11}

V PHYSICAL STATUS

A THYROID

Normal contour, ✓ enlarges very gradually ✓ bilateral involvement, may surround trachea, may be smooth or ✓ nodular never very ✓ hard ✓ adjoining tissues are not affected

B LYMPH GLANDS

✓ Normal

VI LABORATORY DATA ✓ Normal, but basal metabolic rate may be elevated

VII ROENTGENO

GRAPHIC FINDINGS ✓ Tracheal narrowing may be demonstrated⁹

VIII ETIOLOGY

A UNKNOWN

✓ B THEORIES

- 1 Early stage of Riedel's struma^{2 4}
- 2 Dietary deficiency¹¹

✓ Fibrous tissue forms pseudobulules

8 Colloid material

a Scant

b Absent

✓ 9 Cut surface

a Meaty appearance

b Yellowish white or pale pink

c Trabeculated

d Uniform

IX PATHOLOGY^{10 12 13 16}

A GROSS—THYROID (see Fig 143)

- ✓ 1 Size—enlarged moderately
- ✓ 2 'Circular' form of goiter common
- ✓ 3 Consistency
 - a Hard
 - b Rubbery
- ✓ 4 Muscular or fascial tissue are not adherent
- ✓ 5 Capsule
 - a Thickened
 - b Freely movable
- ✓ 6 Color
 - a Whitish gray
 - b Yellowish pink

B MICROSCOPIC—THYROID

1 Acini (see Figs 141 and 142)

✓ a Totally destroyed

✓ b Atrophied

c Variable

(1) Size

(2) Shape

✓ d Colloid

(1) Absent

(2) Scant

✓ 12 Epithelium

a Flat or low columnar, according to amount of colloid

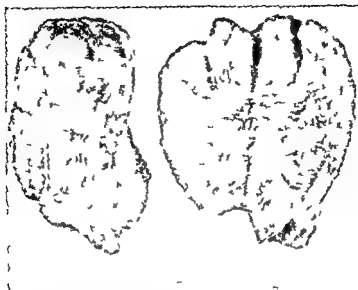


FIG 141 HASHIMOTO'S STRUMA Small lobulations due to lymphoid infiltration Specimen 11 x 12 cm (See low power microscopic view in Figure 142)

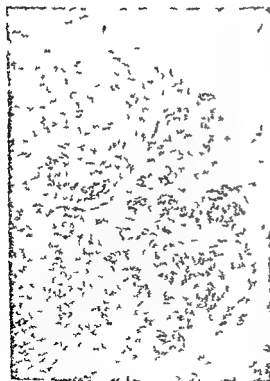


FIG 142 HASHIMOTO'S STRUMA
Microscopic section (x 29)



FIG 143 HASHIMOTO'S STRUMA Few follicles present without colloid Majority of cells are lymphocytes (x 300)

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SECTION 24

CRETINISM

SYNONYMS

Endemic cretinism
 Congenital athyrosis
 Thyro aplasia

Sporadic cretinism
 Infantile myxedema
 Childhood myxedema

I DEFINITION

The term 'cretinism' as used here includes the various types of thyroid deficiency which are listed above as synonyms⁴⁵ Thyroid hypofunction occurring late in pre natal life or during the postnatal growth period which if of sufficient degree and duration, results in characteristic physical and mental changes The condition may be associated with goiter so that return of normal thyroid or excess thyroid hormone secretion may occur when goiter or responsive thyroid tissue is not present spontaneous recovery is impossible

II APPEARANCE

Dull stupid expression depression of the base of the nose, puffiness and wrinkled skin about the eyes thick tongue pot belly retarded growth and development Abnormalities depends on age of onset and duration of thyroid deficiency (see 15 III Figs 145 and 146)

III AGE

Begins in intra uterine life infancy childhood or puberty

IV SEX

No predominance

V MENTAL DEVIATIONS

A INTELLIGENCE

May be retarded or only subnormal, depending on age of onset duration and therapy idiots not uncommon¹¹
 32 60 74

B RESPONSIVENESS

Dull slow hypokinetic rarely exceptions (see Fig 153)

C OTHER ABNORMALITIES

Lethargy or sleepiness very little irritability emotional level low, abnormally quiet

VI PHYSICAL STATUS

A NUTRITION

1 Weight

Malnourished rarely

2 Fat distribution

Increased but variable

Excessive amounts about face nape of neck suprasternal region hips mons veneris back of hands and pot belly, may not have unusual findings (see Fig 146)

B HEIGHT

Almost always below normal depending on duration of disease therapy and family height (see Prognosis and Therapy)

C EXTREMITIES

1 Upper

Proportionate to height in nervous type right angle flexion of upper limbs¹⁶

a Hands

Stubby spatulate pudgy in older cases (see Fig 147)

b Fingers

Stubby

c Span

Normal

SECTION 23

INFECTIOUS GRANULOMATA

I TUBERCULOSIS^{1 4 6}

A SUMMARY

- 1 Occurrence—extremely rare
- 2 Diagnosis is usually made by histologic examination
- 3 Miliary type is more frequent than the caseous form
- 4 If recognized irradiation is advisable

II SYPHILIS^{3 4}

A SUMMARY

- 1 Occurrence—uncommon
- 2 Diagnosis is usually made by histologic examination

- 3 Development during secondary stage gummata are rare
- 4 No clinical importance as regards thyroid
- 5 Tracheal compression may occur
- 6 Antiluetic treatment indicated

III AMYLOIDOSIS⁷

A SUMMARY

- 1 Occurrence—extremely rare
- 2 Etiology as for amyloidosis elsewhere
- 3 Thyroid gland
 - a Consistency—abnormal
 - b Enlarged

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FIG 144 SYPHILIS OF THYROID Age 49 female Syphilis of thyroid causing tracheal compression and stridor Thyroid gland is hard and fixed Response to antiluetic therapy and widening of compressed area to two thirds normal lumen in 1 year No biopsy Positive Wassermann Treated with iodobismuth

3 Blood pressure	Variable often normal or slightly decreased pulse pressure
4 Peripheral arteries and veins	Slow (NOTE children's rate always higher than adults)
5 Vasomotor	Retarded or sluggish response
J BREASTS	
1 Male	Normal
2 Female	May appear normal, but without postpuberal areolae
K ABDOMEN	
	Protuberant
1 Liver	Normal rarely enlarged ³³
2 Spleen	Normal
3 Hernia	Umbilical common ²³
4 Tumor	None
L GENITALIA	
1 Male	
a Penis	Not fully developed unless recovery of thyroid function occurs rarely excessive size ⁵¹
b Testes	Development or descent may be dependent on recovery of thyroid function
c Prostate	Development dependent on same factor (see also result of treatment)
2 Female	
a External	Underdeveloped
b Internal	Underdeveloped
M NEUROMUSCULAR	
1 Muscles	Some hypotonicity
2 Gait	Delayed walking, clumsy waddling in "nervous cretinism" stiff gait may ambulate on their toes with "bobbing" motion some cannot walk or stand ⁴⁶
3 Body movements	Slow in "nervous cretinism" spasticity of both extremities (due to tetany) ⁴⁶
4 Tremor	None
5 Paresthesias	None
6 Reflexes	Normal or very sluggish increased in "nervous type"
N SPEECH	
	Drawl may stutter, or mute ⁴

VII LABORATORY DATA

A URINARY FINDINGS	
1 General	Normal
2 Special chemical analyses (see 25 VII A 2)	
a Sugar	Absent
b Albumin	May be present
c Nitrogen	Decreased ⁵⁴
d Creatine	Absent or diminished ^{6 9 2 3 4 49 5 6 8}
e Creatinine	Normal or may be considered low for skeletal age ^{9 79}
f Sodium	As in myxedema
g Potassium	As in myxedema
h Calcium	As in myxedema ⁵⁴
i Phosphorus	As in myxedema ⁵⁴
j Chlorides	Normal or decreased ¹⁷
k Iodine	Decreased ²³
B HEMATOLOGY	
1 Red blood cells	Normal or decreased
2 Hemoglobin	Normal or slightly decreased

- 2 Lower
- a Feet
- b Toes
- D SPINE
- E INTEGUMENT
- 1 General
- a Texture
- b Temperature
- c Moisture
- d Eruptions
- e Pigmentation
- f Color
- 2 Hair (see Figs 148 and 149)
- a Head
- b Facial
- c Axillary
- d Pubic
- e Body
- F HEAD
- 1 Shape and size
- 2 Facial expression
- 3 Eyes
- a General
- b Fundi
- c Visual
- (1) Fields
- (2) Acuity
- 4 Ears and nose
- 5 Mouth and throat
- a General
- b Teeth
- c Larynx (voice)
- G NECK
- 1 General
- 2 Thyroid
- H CHEST
- I HEART AND PERIPHERAL VESSELS
- 1 Heart
- 2 Rate and rhythm
- Not remarkable, proportionate to height, knock knee or widely separated in 'nervous type'⁴¹
- Flat feet in some
- As fingers
- Normal or scoliosis possible, lordosis common
- Scaling coarse nonpitting edema, wrinkled (see Fig 169, p 421)
- Decreased, may feel cool to touch
- None
- Not usual, eczema in some
- Cafe au lait occasionally general or patchy
- Pale, slight yellowish tinge cheeks may be pink
- Dry fine, brittle
- Little change, may be increased at hairline eyebrows very scant
- May be absent
- Absent usually
- Normal but may be increased⁴²
- Foreshortened naso occipital diameter
- Dull monkey face⁴³ whimsical, grimaces occasionally morose
- Tupiness about eyes palpebral fissures may be narrowed pig eyed nystagmus with nervous type⁴⁴ internal strabismus⁴⁵ (see Mongolism 94 VIF 3)
- Normal
- Normal
- Normal
- Deafness may occur 'depression of nasal base
- Tongue often large and protruding, may drool lips are thick palate narrow and vaulted
- Deciduous teeth retained late causing delayed eruption of permanent teeth resistant to caries, ridging⁴⁶
- Hoarse often rasping
- Not unusual appears short and thick
- Normal not palpable or goiter of various sizes often tremendous nodular soft or firm tracheal compression or deviation may occur may be wholly or partially intrathoracic (see Fig 146)
- Normal breathing may be very slow or stridulous
- Not usually remarkable may show enlargement and rarely evidence of congestive failure⁴⁷
- Normal but bradycardia usual

8 Electroencephalogram	Fewer alpha waves than normal ² brain metabolism retarded ²¹
F URINARY HORMONE ASSAYS	
1 FSH	Normal or rarely positive ³²
2 LH	No data
3 Estrogens	Decreased
4 Pregnanediol	Negative
5 17 ketosteroids	Decreased, about 2 to 4 mg/24 hrs ^{4 43 44}
6 11 oxysteroids	No data
7 Aschheim Zondek	Negative
8 TSH	Positive, ⁶⁴ but results variable may remain slightly positive even after treatment
G BIOPSY	
1 Endometrial	No data could be normal occasionally
2 Testicular	Variable may be normal
H VAGINAL SMEAR	Normal or hypoestrogen effect
I SEMEN ANALYSIS	Decreased count ⁵

VIII ROENTGENOLOGIC FINDINGS

A SKULL (see Fig 154)	
1 Cranial vault	Increased density ³⁹ late closure of fontanelles cranial base shortened developmental deficiency lies in occipital parietal bones and a little in the frontal area sphenoccipital synchondrosis causes 'monkey face'
2 Sella turcica	Enlarged (see 2 XIV G 5a)
3 Mandible	Normal may be retarded ⁷⁰
4 Sinuses	Normal some small
5 Teeth	Retained deciduous teeth ^{70 68 71}
B EPIPHYSEAL STATUS (bone age)⁶⁹	
1 At birth or during first year of life in congenital athyreosis	Fetal stage shown by absence of centers of ossification in pelvis and lower end of femur
2 Older children	A lag of 10 years or more depending on the duration of the disorder before treatment
3 If within 2 years of its onset	Normal limits although often on the low side
4 Previously treated cases	May not be retarded
5 With goiter and return of normal thyroid function	Chronologic age may be approached
C LONG BONES	Thickened cortices radii are shorter than average ⁸⁰
D VERTEBRAE	Development delayed
E BONE TEXTURE	
1 General	Coarse trabeculae
2 Osseous centers	Retarded development fragmented appearance ⁸⁰
3 Cartilages	Multiple irregular islets of ossification which enlarge to form spongy, porous fluffy masses all centers of endochondral ossification may be affected, osteochondritis common (see Fig 156) ^{1 19}
4 Epiphyses	Dysgenesis often present delayed bony union of epiphysis and diaphysis plate hard densely calcified (see Figs 150 and 155) ^{5 13 22 39 4 77 78 80}

3 White blood cells	Normal or slightly decreased
4 Differential	Decreased polymorphonuclear neutrophils increased monocytes or eosinophils but of no clinical importance
C BLOOD CHEMICAL ANALYSES	
1 Sugar	Normal (but low average)
2 Nonprotein nitrogen	Normal, increased rarely ³²
3 Protein (plasma)	Normal or increased to 8 or 8.5 Gm % ^{33 41}
a Albumin	Normal
b Globulin	Increased
c Beta globulin	Increased (compared with adult standards)
d Gamma globulin	Increased (compared with adult standards)
e A/G ratio	Reversed
f Fibrinogen	Normal
4 Uric acid	Normal or decreased ³¹
5 Cholesterol	Increased usually ^{4 33 34 37 38}
6 Sodium	Normal
7 Potassium	No data
8 Calcium	Normal
9 Phosphorus	Decreased ⁷
10 Chlorides	Normal
11 Phosphatase	Decreased ^{30 33 34 37}
12 Iodine	Low total and plasma bound ^{30 40 41}
13 Creatine	Decreased
14 Creatinine	No data
15 Magnesium	Probably as for myxedema
16 Lipids (serum)	Increased ³¹
D FUNCTION TESTS	
1 Tolerance	
a Glucose	
(1) Oral	Variable results ^{14 3 37 41}
(2) Intravenous	Decreased
b Glucose insulin	Increased sensitivity
c Insulin	Increased sensitivity
d Iodine	Decreased
e Creatine	Increased or decreased for chronologic age, but normal for skeletal age ^{3 30 7}
2 Adrenal water	Normal
3 Salt deprivation	Normal
4 Balance	
a Nitrogen	Positive (on initial therapy—negative balance, later increased—see Chart 38) ^{33 36 4 39}
b Calcium	Positive
E MISCELLANEOUS	
1 Basal metabolic rate	Usually low unless spontaneous improvement in cretins with goiter (see below)
2 Circulation time	No data—see 25 VII E 2
3 Sedimentation rate	Normal
4 Specific dynamic action of protein	See 25 VII E 4
5 Gastric analysis	See 25 VII E 5
6 Electrocardiogram	T waves variable— ³⁶
7 Blood volume	Decreased

XII SYMPTOMATOLOGY

A GENERAL

- 1 Retardation of
 - a Growth
 - b Mental faculties
 - c Sexual development
- 2 Goiter may be present
- 3 Skin
 - a Dry
 - b Scaly
 - c Coarse
 - d Yellowish tinge in some
 - Pale

B NEUROMUSCULAR AND SENSORY

- 1 Deafness
- 2 Mutism
- 3 Sleepiness
- 4 Lethargy
- 5 Fatigue
- 6 Weakness
- 7 Muscular hypotonia
- 8 Cold sensitivity
- 9 Tremors, late in disease if central nervous system affected
- 10 Tetany (India)¹⁰

C GASTRO INTESTINAL

- 1 Infant may have difficulty in nursing or taking feedings as well as swallowing due to
 - a Tongue enlargement
 - Substernal goiter
 - c Pressure on the larynx from the goiter
- 2 Constipation
- 3 Anorexia
- 4 Weight gain uncommon

XIII DIAGNOSIS

A INTRODUCTION

- 1 Clinical differentiation of thyroid deficiency as listed at the beginning of the chapter depends on age of onset
 - At or before birth
 - (1) Congenital athyreosis or thyro aplasia
 - (a) Endemic
 - (b) Sporadic
 - (2) Cretinism with goiter
 - (a) Endemic
 - (b) Congenital or sporadic
 - b After birth—1 to 15 years
 - (1) Infantile myxedema

- (a) With goiter
- (b) Without goiter
- (2) Childhood myxedema
 - (a) With goiter
 - (b) Without goiter

B UNTREATED CRETIN (see 24 \II)

- 1 Mentally sluggish rare exceptions
- 2 Height age—decreased, depending on same factors as bone age (see I V A)
- 3 Bone age—retarded if disease ■ of sufficient duration
- 4 Sexual development—delayed
- 5 Cholesterol (plasma)—elevated usually
- 6 Iodine (serum organic)—decreased
- 7 Basal metabolic rate—low when obtainable¹⁷
- 8 Sella turcica—enlarged
- 9 Therapy produces striking response

C TREATED CRETIN (see Table 15)

- 1 Previous or concurrent treatment may make the diagnosis difficult because
 - a Mental retardation—may be slight
 - b Growth resumption takes place at a normal or accelerated rate
 - c Height age—corrected to a certain degree
 - d Bone age—lag may have been overcome
 - e Sexual development—may have occurred
 - f Normal values for
 - (1) Cholesterol (plasma)
 - (2) Iodine
 - (3) Basal metabolic rate
- 2 Prior inactive growth period should be proved
- 3 Sella measurement is helpful when enlarged (see 2 \IV G)
- 4 If the total evidence is
 - a Impressive continue with desiccated thyroid
 - b Inadequate
 - (1) Omit desiccated thyroid for 1 to 2 months
 - (2) Observe patient for development of
 - (a) Mental sluggishness
 - (b) Growth arrest
 - (c) Dry skin
 - (d) Cholesterol (plasma)—increase
 - (e) Basal metabolic rate—decrease

F MISCELLANEOUS

- | | |
|-----------|--|
| 1 Trachea | May be compressed in any direction by large goiter |
| 2 Chest | Heart size normal or enlarged |

IX ETIOLOGY

A PRENATAL

- 1 Congenital
 - Athyrosis—there may be germ cell
 - (1) Defect—questionable cause
 - (2) Injury by goitrogenic agents
 - b Goiter
 - (1) Predisposition factors
 - (2) Unknown goitrogenic agents
- 2 Endemic goiter (see 15)

B POSTNATAL

- 1 Endemic or congenital goiter with failing secretory function
- 2 Iodine deficiency or administration (see Fig 157 Chart 35)
- 3 Antithyroid drugs
- 4 Irradiation
- 5 Thyroidectomy
- 6 Thyroiditis
- 7 Thyroid atrophy due to pituitary deficiency

X PATHOLOGY

A GROSS

- 1 Thyroid
 - a Complete absence, except for a few follicles^{15 18 1 43 45}
 - b Colloid adenoma with hyperplasia
 - c Colloid fetal embryonal adenoma
 - d Nodular goiter
 - Simple goiter
 - f Diffuse hyperplasia
 - g Mixed
- 2 Pituitary
 - a Normal
 - b Hypertrophy¹⁸—weight from 0.7 to 2.42 Gm (average normal 0.6 Gm)
 - c Atrophy (rare)^{18 28}
- 3 Adrenals—normal
- 4 Gonads—small
- 5 Pancreas—normal
- 6 Thymus
 - a Normal
 - b Aplasia
- 7 Brain
 - a Size
 - (1) Normal
 - (2) Decreased somewhat
 - b Chronic meningeal alterations
 - Hydrocephalus (slight)

B MICROSCOPIC

- 1 Without goiter (see 24 \ A 1)
 - a Complete fibrosis in some
 - b Parenchyma—variable amount, but always decreased
 - c Lymphocytic infiltration common
- 2 With goiter—many variations from hyperplasia to cirrhosis (see 24 \ A 1 Figs 158 and 159)⁴⁰
- 3 Pituitary—see 2 IV B 14
- 4 Bones
 - Dense
 - b Marrow very rich in fat
- 5 Muscles—hyaline degeneration

XI PATHOLOGIC PHYSIOLOGY

A SUMMARY

- 1 Essentially similar to adult myxedema with certain exceptions (see 24 \ I)
- 2 Anterior hypophysis increases in size with thyroid failure
- 3 Pituitary eosinophilic cells
 - a Decrease
 - b Disappear
- 4 Growth hormone secreted by eosinophilic cells, decreases and is probably the chief cause of growth retardation
- 5 Injection of growth hormone stimulates growth in animals that are
 - a Hypophysectomized
 - b Thyroidectomized
- 6 Long standing thyroid deficiency may ultimately decrease all pituitary function from lack of thyroid hormone by affecting the pituitary cells directly (cretins with thyroid atrophy)
- 7 Administration of desiccated thyroid may cause resumption of growth and nitrogen retention by reestablishing eosinophils to secrete growth hormone
- 8 Failure of growth with desiccated thyroid administration may indicate a nonresponsive pituitary (see 6 above)
- 9 Pituitary thyrotropic hormone
 - Increases with decreased thyroid function
 - b Stimulates thyroid function possibly in cretins with goiter in whom reponsive thyroid tissue is present

(4) Bone age

- (a) Increases rapidly
- (b) Progresses disproportionately to increase in height age
- (c) May become normal for chronologic age

(5) Goiter, if present, may decrease in size^{34, 35}

(6) Hair

- (a) Growth may be stimulated
- (b) Hypertrichosis may disappear

(7) Sexual development

- (a) Breasts enlarge
- (b) Menarche may be initiated
- (c) Reproductivity probably normal

(8) Urine

- (a) Creatine — increases^{36, 37, 38}

- (b) 17 ketosteroids — may remain low³⁹

(9) Blood chemical analyses approach normal range for

- (a) Cholesterol (plasma)
- (b) Iodine (organic)

2 Methyltestosterone (see Chart 38)

- a Indication — if no response with desiccated thyroid
- b Dosage — oral, 10 to 20 mg daily
- c Results
 - (1) Growth may be stimulated
 - (2) Basal metabolic rate may increase

3 Thyrotropic hormone

- a Effective if responsive thyroid tissue is present
- b Not available for clinical use

4 Growth hormone

- a Indicated in cases who fail to grow with desiccated thyroid
- b Not available for clinical use

II SURGICAL—Indications

- 1 Goiter, if
 - a Unsightly
 - b Tracheal compression is found
- 2 Evidence suggesting malignancy

C COMPLICATIONS

- 1 Anemia
 - a Thyroid medication usually restores blood count to normal
 - b Iron may facilitate response
- 2 Hyperthyroidism (see 15, 24 VI A)

XVII PROGNOSIS

A WITHOUT TREATMENT (see Figs 164 167)

- 1 Absence of goiter
 - a Permanent state
 - b Mentality remains low
 - c Dwarfism
- 2 Presence of goiter
 - a As above
 - b Lesser degrees of mental and physical retardation
 - c Spontaneous recovery of normal or excess thyroid function with corresponding improvement depending on
 - (1) Duration before recovery
 - (2) Degree of deficiency

II WITH TREATMENT (see Figs 145 152 162 and 163)

- 1 Factors
 - a Degree of deficiency
 - b Therapy depending on
 - (1) Time instituted
 - (2) Responsiveness
 - (3) Adequacy
- 2 Results — see 24 VI A 1 c
- 3 Life expectancy normal

XVIII CAUSES OF DEATH

A UNTREATED

- 1 Premature aging
- 2 Intercurrent infection

B TREATED—No data

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TABLE 15 THYROID DEFICIENT CHILD

	UNTREATED	TREATED WITH THYROID (DESICCATED) ■ SPONTANEOUS RETURN OF THYROID FUNCTION
Height age	Retarded	Less retarded
Bone age	Greater delay than height age	Chronologic age reached if treated before age of 10
Mental age	Subnormal in majority	Some improvement but remain below average
Mental activity	Sluggish (and hypokinesia)	Normal
Cholesterol (pls ma)	High	Normal
Dental age by roentgenograms	Normal deciduous teeth remain	Normal deciduous teeth expelled
Sella turcica	Enlarged	Size increases with skeletal growth

D CRETINISM WITH EUTHYROIDISM (see Table 15 Figs 151 and 160)

- 1 Past history of thyroid deficiency
- 2 Goiter—always present
- 3 Height age—subnormal
- 4 Bone age—may approximate height age
- 5 Sexual development—normal

13 Discrete fetal adenoma may develop into malignant degeneration

14 Anemia (secondary)

15 Albuminuria

XVI TREATMENT (see Chart 39)

A MEDICAL

1 Desiccated thyroid (U S P)

a Comment

- (1) Medication can be given with very little danger in the young
- (2) Dose may be reduced if child becomes restless or irritable

b Dosage

- | | |
|----------------------|---------------------------------|
| | GR DAILY |
| (1) First 6 months | $\frac{1}{16}$ to $\frac{1}{8}$ |
| (2) Up to 3 years | $\frac{1}{8}$ to $\frac{1}{4}$ |
| (3) Three to 9 years | 1 |
| (4) Nine to 18 years | 1 2 |

c Results²⁴

- (1) Mental state
 - (a) Responsiveness improves
 - (b) Mental age advances
 - (c) Normal intelligence in few
 - (d) Aptitude ■ generally low
 - (e) Idiocy occasionally
- (2) Growth rate (see Charts 36 37 and 39)
 - (a) Initially—increases
 - (b) Later — follows normal trend for height age
- (3) Final height
 - (a) Predestined height minus approximately that lost while thyroid deficient
 - (b) Growth rate cannot be forced by overtreatment because of epiphyseal closure

E CRETINISM WITH HYPERTHYROIDISM (see Table 15, Figs 150 and 161)

- 1 Hyperthyroid signs and symptoms
- 2 Goiter—always present
- 3 Height age—subnormal
- 4 Bone age—may approach chronologic age
- 5 Sexual development—normal

XIV DIFFERENTIAL DIAGNOSIS

A DWARFISM—see 91 IV, 92 95

XV COMPLICATIONS SEQUELAE AND ASSOCIATED DISEASES

A SUMMARY

- 1 Mental disorders
- 2 Final height—see 24 XIII
- 3 Reproductive system
 - a Sexual development—delayed
 - b Sterility in majority, but may be come pregnant⁷⁰
- 4 Deafness
- 5 Mutism
- 6 Tremor
- 7 Spasticity
- 8 Tetany (India)⁴⁶
- 9 Cardiac decompensation⁴⁴
- 10 Constipation (may be severe)
- 11 Infections—very common
- 12 Hyperthyroidism³

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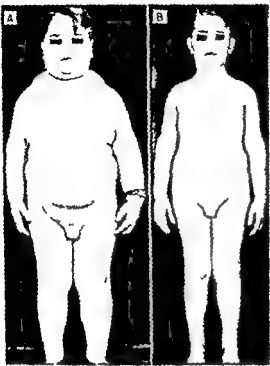


FIG 146 CRETINISM (Left) Age 14 Substernal goiter (congenital) and concurrent thyroid deficiency before treatment Plasma cholesterol 360 mg % BMR minus 36% (Right) After 14 months treatment (Hurxthal L M and Musulin N Cretinism Am J Med 1 66 82)

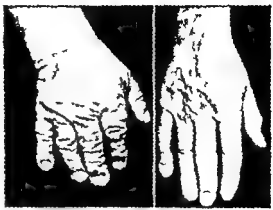


FIG 147 CRETINISM (Left) Hand of adult cretin (Right) Normal hand for comparison (de Quervain F and Wegelin C Der endemische Kretinismus Berlin Springer p 52)



FIG 145 CRETINISM (*Left*) Cretin with recurrent thyroid deficiency at 21 months having begun at 4 months of age and necessitating gastrostomy because of dysphagia thyroid palpable Note nodular goiter in mother (*Right*) Same patient at 12 years Irregular treatment prior to admission (Burroughs Well come thyroid $\frac{1}{4}$ gr daily = equivalent to 1/10 gr USP) Treatment thereafter was adequate in dose but taken irregularly Idiocy Sella size 63 sq mm (Hurxthal L M and Musulin N Cretinism Am J Med 1 72 82)

FIG 149 CRETINISM—CONGENITAL ATHYREOSIS

Family history Negative

History of present illness Normal at birth At 6 months of age developed constipation which required hospital care Cretinism was recognized and desiccated thyroid was prescribed but in irregular and inadequate dosage At 15 years of age the child was only in the fifth grade

Physical examination Age 15 Weight 93 lbs Height 50½ in BP 96/60 Pulse 72 Sluggish mentally Tongue large thick Marked hair growth on back and legs Skin dry waxy pallor Thyroid not palpable

Laboratory data RBC 4 000 000 Hgb 72% Total protein 13 Gm % Plasma cholesterol 263 mg %

Röntgenographic findings Bone age 8 years 3 months Sella turcica 121 sq mm (enlarged) Numerous unerupted permanent teeth Twelve year molars unerupted

Treatment Desiccated thyroid 1 gr daily orally

Progress Growth of 4½ in in 11 months Weight 84 lbs Pubic and axillary hair developed but marked loss of body hair Total protein 6.7 Gm % Plasma cholesterol 158 mg % Bone age 10 years 9 months

(Top left) Before treatment

(Top right) One year later

(Bottom left) Photograph of hair on back before treatment

(Bottom right) Picture shows persistence of hair loss after a year

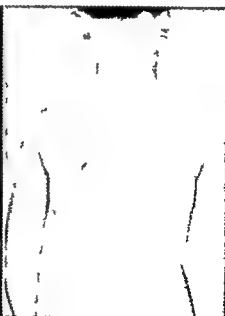
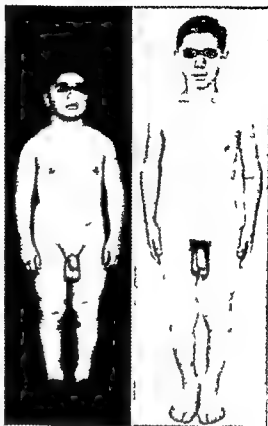




FIG 148 CHILDHOOD MYXEDEMA WITH EXCESS HAIR GROWTH—RESPONSE TO DESICCATED THYROID

Chief complaints Retarded growth and mentally slow for 2 years

History of present illness No other complaints Menarche at 12 but irregular and scanty periods

Physical examination Age 13 years 9 months Weight 109 lbs Height 57 in Span $49\frac{3}{4}$ in Height age 12 years Movements slow Edema of face Excess hair on neck side of face back and legs Marked hyperkeratosis of knuckles elbows and knees

Laboratory data Plasma cholesterol 225 mg % Serum phosphorus 3.8 mg % 17 keto steroids 6.3 mg /24 hrs

Roentgenographic findings Bone age 13 years 9 months

Treatment Desiccated thyroid $1\frac{1}{2}$ gr daily for 3 months Plasma cholesterol 156 mg % Serum phosphorus 3.6 mg %

Progress Periods regular 5 days Skin smooth Loss of excess hair Weight 99 lbs Height $51\frac{1}{4}$ in

Comment This is one of several cases in which marked hirsutism accompanied myxedema and disappeared with treatment. The normal bone age and the relatively slight increase in plasma cholesterol are interesting. The loss in weight has masked the growth increase the latter being only $\frac{1}{4}$ in in 3 months. (Left) Before therapy (Right) Three months later

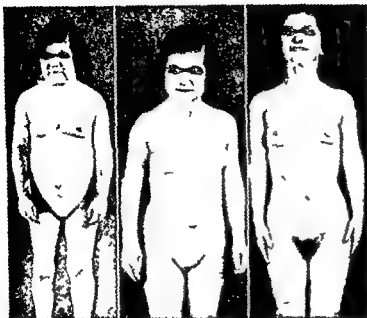


FIG 152 CRETIN Age 17 Irregularly and inadequately treated Onset in infancy no palpable thyroid presumably congenital atrophy (Left) Before institution of adequate therapy Plasma cholesterol 430 mg % BMR minus 18% Lone age 11½ years (Center) After 3 months of treatment 10 g of desiccated thyroid per week (Right) After 1 year of treatment Height 49½ in at 18 2 years later 53½ in Pregnancy occurred later with normal baby For bone changes see Figure 155 (Huruthal L M and Musulin N Cretinism Am J Med 16 87)

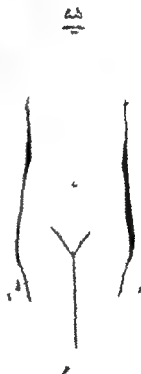


FIG 153 CRETIN (See also Fig 154 Chart 37) Cretin with concurrent thyroid deficiency and a palpable thyroid gland of colloid type before treatment Age 11 years Height age 5½ years Bone age 7½ years Plasma cholesterol 3.6 mg % BMR minus 32% There was no apparent retardation in mental age the child was mentally alert (Huruthal L M and Musulin N Cretinism Am J Med 16 87)

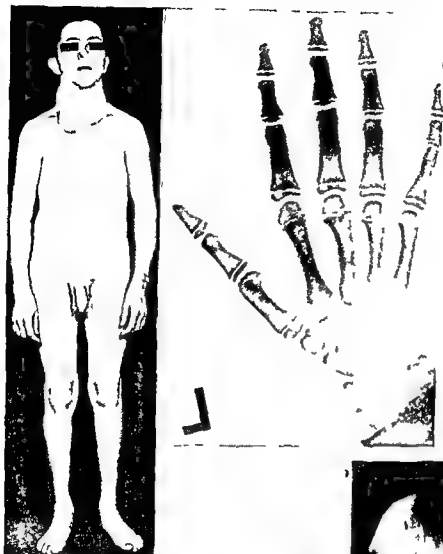


FIG 150 CONGENITAL GOITER Congenital goiter with antecedent thyroid deficiency and concurrent hyperthyroidism. At age 18 height age 12 years bone age 13 years. Increase in size of goiter beginning at age 16 with spurt in growth. Greater activity of thyroid in the past 2 years caused the bone age 13 to approximate the height age 12 (Hurxthal L M and Musulin N. Cretinism. Am J Med 1 66 82)

FIG 151 CRETINISM Age 38 Goiter since birth. Intra-thoracic goiter with pressure on trachea. Entered school at 9 finished at 24. Weight 88 lbs Height 56 in BMR plus 6%. Goiter was removed. Pathologic report: multiple colloid adenomatous goiter with secondary hyperplasia. Example of cretinism with subsequent normal function. Postoperative plasma cholesterol 324 mg %. Clinical thyroid deficiency corrected with desiccated thyroid. Bella measured 74 sq mm which is above average for height age of 12.



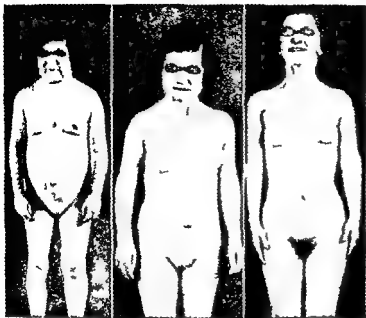


FIG 152 CRETIN Age 17 Irregularly and inadequately treated. Onset in infancy; no palpable thyroid presumably congenital athyreosis (Left) Before institution of adequate therapy Plasma cholesterol 450 mg % BMR minus 18% Bone age 11½ years (Center) After 3 months of treatment 10 gr of desiccated thyroid per week (Right) After 1 year of treatment Height 49½ in at 17 2 years later 53½ in Pregnancy occurred later with normal baby For bone changes see Figure 155 (Hurthall L M and Musuhn N Cretinism Am J Med 16 82)

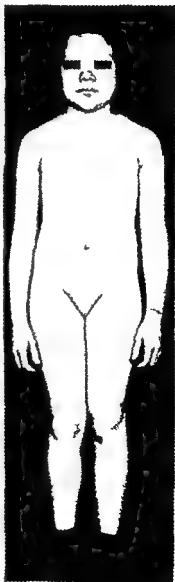


FIG 153 CRETIN (See also Fig 154 Chart 3.) Cretin with concurrent thyroid deficiency and a palpable thyroid gland of colloid type before treatment Age 11 years Height age 8½ years Bone age 7½ years Plasma cholesterol 3.6 mg % BMR minus 3% There was no apparent retardation in mental age the child was mentally alert (Hurthall L M and Musuhn N Cretinism Am J Med 16 82)



FIG 154 CRETIN (See also Fig 153)
Skull of a cretin showing an enlarged sella
Sella measures 11 mm deep and 11 mm
anteroposteriorly Average normal measure-
ments for this age (11 years) are 9.36 by
6.18 mm (Hurthall L M and Musulin N
Cretinism Am J Med 1 78 82)

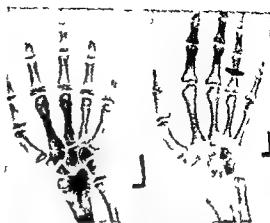


FIG 155 ROENTGENOGRAM OF A CRETIN'S
HAND (See also Fig 152) (Left) Age 17
female with concurrent thyroid deficiency
in which previous treatment was inadequate
(Right) After 3 years of treatment com-
plete epiphyseal closure Note dense and
widened phalangeal bones due to long-
standing hypothyroidism Height age at 18
years was 8 years at 20 10 years Puberty
began during the first year of treatment
(Hurthall L M and Musulin N Cre-
tinism Am J Med 1 67 82)



FIG 156 CRETINISM Juvenile osteochon-
dritis deformans in cretinism (de Quervain F
and Wegelin C Der endemische Kretin-
ismus Berlin Springer p 47)

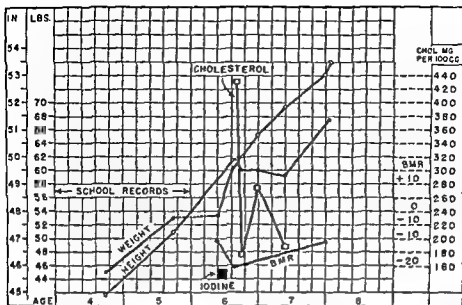


CHART 35 IODINE INDUCED MYXEDEMA (See also Fig 157) Effect of iodine administered to child of 6 with colloid goiter resulting in clinical myxedema with high plasma cholesterol and low BMR. The unusual effect suggests colloid goiter with some areas of hyperplasia or hyperplasia alone which became involuted when iodine was given. The weight and the height curves suggest a preexisting mild hyperthyroidism even though the BMR recorded was minus 11% (Hurxthal L. M. Myxedema and its various causes. S. Clin North America 25 657 671)

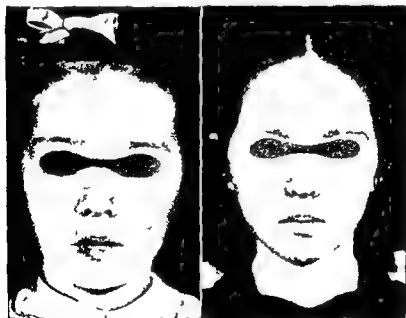


FIG 157 MYXEDEMA From administration of iodine in a girl of 6 with colloid goiter. (See also Chart 35) (Left) After taking Lugol's solution 5 to 10 drops daily for months. Weight 61 lbs. Pulse 76. Plasma cholesterol 432 mg %. BMR minus 21%. (Right) After discontinuing iodine. Weight 60 lbs. Pulse 104. Plasma cholesterol 1.9 mg %. Subsequent course normal. Gland continued to be easily palpable and felt like a colloid gland. Eight year follow up—patient normal in every way (Hurxthal L. M. Myxedema and its various causes. S. Clin North America 25 657 671)



FIG 154 CRETIN (See also Fig 153) Skull of a cretin showing an enlarged sella. Sella measures 11 mm deep and 11 mm anteroposteriorly. Average normal measurements for this age (11 years) are 9.36 by 6.18 mm (Hurxthal L M and Musulin N. Cretinism Am J Med 1:78-82).

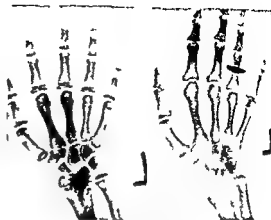


FIG 155 ROENTGENOGRAPHY OF A CRETIN'S HAND (See also Fig 152) (Left) Age 17 female with concurrent thyroid deficiency in which previous treatment was inadequate (Right) After 3 years of treatment complete epiphyseal closure. Note dense and widened phalangeal bones due to long standing hypothyroidism. Height age at 18 years was 8 years at 20 10 years. Puberty began during the first year of treatment (Hurxthal L M and Musulin N. Cretinism Am J Med 1:67-82).



FIG 156 CRETINISM Juvenile osteochondritis deformans in cretinism (de Quervain F and Wegelin C. Der endemische Kretinismus Berlin Springer p 47).

FIG 161 CRETINISM WITH CONCURRENT EUTHYROIDISM AND SUBSEQUENT HYPERTHYROIDISM Age 11 male Height age 7 years Bone age 5 years Mentally alert no evidence of concurrent thyroid deficiency Plasma cholesterol 212 mg % BMR plus 12% The goiter had increased in size before admission and there had been an improvement in growth rate mental and physical activity The retarded height age and bone age are stigmata of previous thyroid deficiency After subtotal thyroidectomy desiccated thyroid was prescribed and taken for several years At age of 22 patient returned with recurrence of goiter and hyperthyroidism (BMR plus 32%) First pathologic report colloid adenomatous goiter Second report (at age 22) colloid adenomatous goiter with areas of hyperplasia (Bartels ■ C. Hyperthyroidism developing in a cretin S Clin North America 25 672 678)



FIG 162 CHILDHOOD MYXEDEMA (Left) Age 13 Duration 1 year Chief complaints languor and weight gain Weight 116 lbs Height age 12½ Bone age 12¾ years Sella measured 9 x 10 mm (average normal 9.6 by 6.8 mm) RBC 3 600 000 Hgb 10% Plasma cholesterol 416 mg % Blood sedimentation rate 60 mm/hr Thyroid uniformly enlarged firm suggesting thyroiditis Patient continued to do well in school despite her lethargy Dislikes cold weather Slight secondary sex development including pubic hair but not catamenia (Right) One year later Treatment 1 gr of desiccated thyroid daily Weight loss of 10 lbs with treatment then recovered to 109 lbs Grew 2¾ in in year (normal rate at this age 1½ in) Menstrual periods began after 3 months of treatment RBC 4 000 000 Hgb 90% Plasma cholesterol 176 mg % Two years later height 62½ in Thyroid normal in size with only slight firmness Patient grew a total of 4 in and changed from 40 to 60 percentile curve of Burgess Weight 116 lbs Plasma cholesterol 182 mg % Sedimentation rate 16 mm/hr Bone age 14 3 years This case illustrates slight lag in bone age because of short duration of thyroid deficiency and regression of enlarged thyroid (Hurxthal L M Cretinism M Clin North America 32 122 139)



FIG 158 CRETINISM (See also Fig 159)
Papilliferous hyperplasia associated with
clinical myxedema in a child Possible effect
of iodine (Klose H Die Chirurgie der
Basedowschen Krankheit Stuttgart Enke
p 319)



FIG 160 CONGENITAL GOITER Sister
of patient shown in Figure 150 previous
thyroid deficiency (cretinism) and con-
current euthyroidism (normal thyroid
function) Age 20 Height age 10½ years
Height 55 in Bone age normal Cata-
menia at 17 years of age Mental status
retarded Plasma cholesterol 1.6 mg %
BMR plus 12% Thyroid deficiency
existed during childhood causing delayed
puberty Function evidently revived
around age of 12 to 15 years (Hurxthal
L M Myxedema and its various causes
S Clin North America 25 657 671)



FIG 159 HISTOL-
OGY OF GOITER IN A
CRETIN Papilliferous
epithelium in large
nodular or endemic
type goiter removed
from a cretinous child

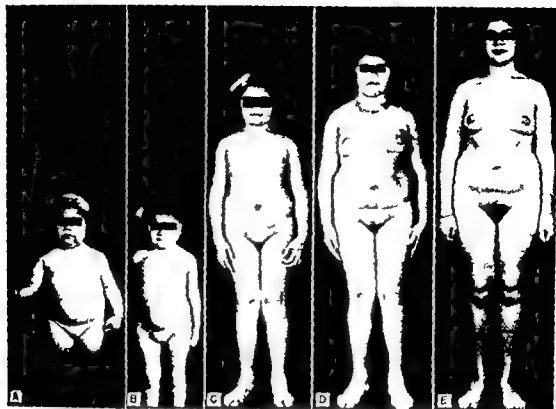


FIG 163 CRETNISM INFANTILE MYXEDEMA OR CONGENITAL ATHYREOSIS (A) Age 7 Unable to walk unaided Marked flat feet and lumbar lordosis Patient had received inadequate and irregular treatment previously Plasma cholesterol 460 mg % BMR minus 26% Bone age 9 months which strongly indicated congenital athyreosis Sella 9 x 13 mm Adequate treatment started (B) Three months later (C) Age 12 (D) Age 16 Patient had not taken thyroid for some time (E) Final result Age 18 Normal intelligence Height age retarded Radial epiphyses closed Sella 11 x 14 mm It is believed that the early (although inadequate) treatment in infancy was responsible for the normal intelligence attained (Hurxthal L M and Musulin N Cretinism *Am J Med* 1 72 82)

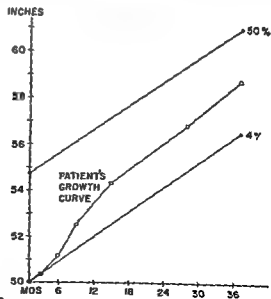


CHART 37 GROWTH IN CHILDHOOD MYX EDEMA (See also Figs 153 154) Note spurt in growth on desiccated thyroid (1 gr a day) and compare with expected growth of normal aver age child of 11 (50% curve of Burgess) and a normal short child of 11 whose height is less than 9 years and falls upon the 4% curve Pa tient has gone from height age of 8 3/5 years at 11 to a height of 11 4/5 years at 13 (in 26 months) After the initial spurt in the first year or so growth rate levels off to normal

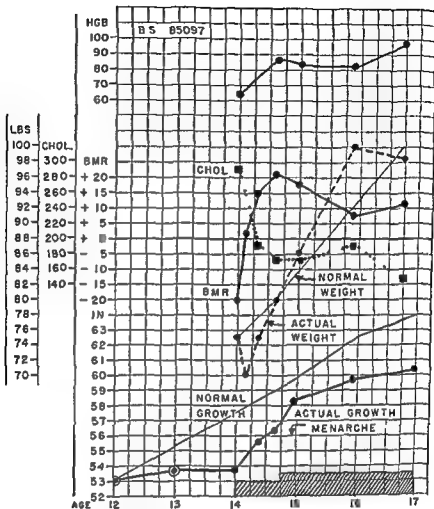


CHART 36 CHILDHOOD MYXEDEMA Age 14 Chart depicts the acceleration of growth on giving desiccated thyroid. The change in plasma cholesterol, BMR, and Hgb are shown. In spite of growth retardation and failure of secondary sex development and dry skin, the patient's mental age or alertness apparently was not retarded. Patient was graduated from college and on thyroid has been normal ever since. On stopping thyroid on one occasion, evidence of thyroid deficiency soon became apparent. Note initial drop in weight and then increase as anabolic effects (stimulation of growth hormone) followed. One shaded block equals 1 gr daily of desiccated thyroid (U.S.P.). Dot in circle indicates height recorded at school.



FIGS 164 (Left) and 165 (Right) CRETINS WITHOUT GOITER (European) (de Quervain, F and Wegelin C Der endemische Kretinismus Berlin Springer, pp 37 and 78)



FIG 166 (Left) CRETIN WITH HANGING GOITER (European)
FIG 167 (Right) CRETIN FROM MOUNTAINOUS AREA WITH SMALL INTRATHORACIC GOITER (European)
(de Quervain F and Wegelin C Der endemische Kretinismus Berlin Springer pp 32 and 33)

CHART 38 CRETINISM Chart shows nitrogen retention (shaded area) on giving thyroid (solid black) to a $4\frac{1}{2}$ year old cretin in spite of weight loss due to extracellular fluid

Period A—actual weight then increased and continued to do so even when thyroid was discontinued and methyltestosterone was given

Period C—note loss of accumulated fluid due to androgen when thyroid given again and greater output of urinary nitrogen

Period K—which may not have represented tissue nitrogen but stored nitrogen Methyltestosterone is said to stimulate growth in cretins unresponsive to thyroid (Wilkins L Conference on Metabolic Aspects of Convalescence 9th meeting Feb 23, New York. Macy pp 160 167)

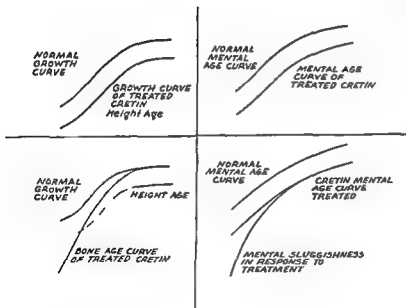
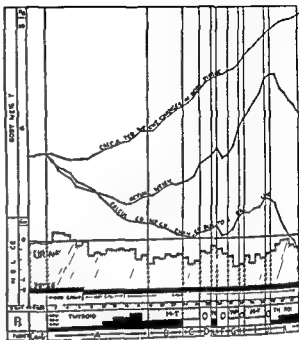


CHART 39 CRETINISM
Diagrammatic illustration of effect of treatment or resumption of normal thyroid function in cretins. The theoretical relationships between height age, bone age and mental activity are shown (Hurxthal L M and Musulin N. Cretinism Am J Med 1 66 82)

b Temperature	Subnormal, cool to touch
■ Moisture	Dry very little sweating
d Eruptions	Psoriasis, atopic eczema xanthomatosis ⁷⁰
e Pigmentation	Patchy cafe au lait
f Color	Yellow, waxy pallor may have pink cheeks
g Nails	Brittle thick slow growth
2 Hair	
a Head	Dry brittle, often fine falls out easily, diffuse or spotty alopecia may be present, poor growth will not hold permanent wave (see Fig 171)
b Facial	Sparse beard eyebrows scant or normal, rarely increased (see Fig 172) ⁷⁷
■ Axillary	Normal scant or absent (see 96 III B C)
d Pubic	Normal scant or absent
■ Body	Normal rarely increased or may be decreased ⁷⁷
F HEAD	
1 Shape and size	Normal, may appear obese because of edema
2 Facial expression	Dull sleepy bloated
3 Eyes	
a General	Puffiness of lids, watery eyes narrow palpebral fissures pig-eyed sometimes
b Fundi	Normal or sclerotic vessels
c Visual	
(1) Fields	Normal
(2) Acuity	Normal occasionally may be diminished
4 Ears and nose	Deafness is common (nerve and/or middle ear) nose may be normal or slightly larger because of subcutaneous edema
5 Mouth and throat	
a General	Lips may appear puffy pale, tongue may be swollen pale or reddish may have glossitis (possible vitamin B deficiency and rarely pernicious anemia)
b Teeth	Normal or tendency to decay
c Larynx (voice)	Hoarse, deep edema of cords
G NECK	
1 General	Normal or fat
2 Thyroid	Usually not palpable except in thyroiditis colloid or nodular goiter may be present hyperplasia may be due to drugs (see 14 IX II 1 d, e, f g 24 IX)
H CHEST	Normal shape and size supraclavicular fat pads pleural effusion occurs occasionally
I HEART AND PERIPHERAL VESSELS	
1 Heart	May be increased in transverse diameter (due to fluid and/or dilatation) apical beat feeble ^{27 43 55 56 78 8, 94 95 101 114 118}
2 Rate and rhythm	Bradycardia often may be normal or even increased in nervous individuals
3 Blood pressure	May be normal low not infrequently elevated when low systolic pressure consider possibility of pituitary origin systolic pressure above 150 in 50 per cent of cases diastolic pressure above 90 in 40 per cent ^{111 113}
4 Peripheral arteries and veins	Normal or slow arteries may be sclerotic

SECTION 25

MYXEDEMA

SYNONYMS

Gull's disease

Primary thyroid deficiency or atrophy

Hypothyroidism

Athyreosis

I DEFINITION

Myxedema is a condition which results from hypofunction of the thyroid gland with marked underproduction of thyroid hormone. It is usually characterized by non pitting edema, especially about the eyes, dry skin, slow pulse, mental lethargy, and is further identified by a low basal metabolic rate, elevated plasma cholesterol and low blood iodine.

II APPEARANCE

Lethargic individual with puffiness about the eyes, bloated (see Fig 168)

III AGE

Any (see Cretinism), but only adult myxedema is described in this section, usually in fourth or fifth decade, average 51±

IV SEX

Females more often affected than males, ratio 4:1

V MENTAL DEVIATIONS

A INTELLIGENCE

Normal variations

B RESPONSIVENESS

Poor, slow, seem hampered

C OTHER ABNORMALITIES

Memory impaired, sluggishness, lethargy, little irritability, emotional response slow, whimsical, rarely psychosis with or without hallucinations or other mental aberrations²

VI PHYSICAL STATUS

A NUTRITION

Good

1 Weight

Variable, normal or below in 40 per cent (see Fig 169)^{1,3}

2 Fat distribution

Pyknic type, uniform distribution, but may show predilection for nape of neck and supraclavicular areas

B HEIGHT

Normal variation

C EXTREMITIES

Normal contours, unless overweight

1 Upper

a Hands

May be edematous and so appear fat, pawlike, cold

b Fingers

Normal

c Span

Normal

2 Lower

a Feet

As hands

b Toes

As fingers

D SPINE

Normal

E INTEGUMENT

1 General

Thickening of subcutaneous tissue causing nonpitting edema may be localized

a Texture

Rough, slight scaling, wrinkling even with edema hyperkeratosis of feet (see Fig 170)

5 Reticulocytes	Normal ⁴
6 Bone marrow	Hypoplasia in longstanding cases ⁸
C BLOOD CHEMICAL ANALYSES	
1 Sugar	Normal or decreased
2 Nonprotein nitrogen	Normal rarely increased
3 Protein (plasma)	Normal or may be increased (up to 8 Gm %) ^{6 98 106} 140 1 1
a Albumin	Normal or decreased ^{95 140 148}
b Globulin	Normal or decreased ^{140 148}
■ Gamma globulin	Decreased ⁹⁸
d Beta globulin	Increased ⁹⁸
■ A/G ratio	Normal or decreased (average 1.21) ^{98 140 148}
f Fibrinogen	Normal ⁹⁸
4 Uric acid	Normal or decreased
5 Cholesterol	Increased in 95 per cent of cases ¹⁴⁸ usually 100 per cent or more elevated depending on the level before onset of myxedema (see Charts 40 41) ^{7 15 6 81 84 73 74 76 9 94}
■ Sodium	Normal
7 Potassium	Normal
8 Calcium	Normal ^{1 4 44 133}
9 Phosphorus	Normal or decreased ^{1 4 41 133}
10 Phosphatase	Normal or decreased ^{14 131}
11 Chlorides	Normal ^{6 140}
12 Iodine	Decreased (total and plasma bound) rarely ^{8 21 4 29 98} 78 101 107 121 1 8 124 137 138 1 8-100 147
13 Creatine	Normal or decreased ^{1 6}
14 Creatinine	Normal
15 Free fat	High ^{61 61}
16 Lipid phosphorus	High, ^{61 60 61} there is no correlation between height of cholesterol and level of neutral fat in serum
17 Magnesium	Normal (serum) but ultrafiltrable fraction above normal and nonfiltrable (bound) fraction ■ absent ²⁷
D FUNCTION TESTS	
1 Tolerance	
a Glucose	Variable may be increased (low curve) (see Table 102) 1 4 40 57 80 81 87 91 99 162
b Glucose insulin	No data
c Insulin	Slow initial fall (insulin resistance) ⁴⁷
d Galactose	
(1) Oral	Increased (flat curve) question of retarded absorption ⁵ 143 11
(2) Intravenous	Normal ¹¹
■ Iodine	More retained in blood stream than normal, average increase 39 per cent curve greater than normal and falls slowly to basal level ^{130 140 122 14 163}
f Creatine	Normal or increased (increases with treatment i.e. 87% average retention of amount ingested) ^{741 1 4 150}
2 Adrenal water	Usually negative (see 6) ⁹⁷
3 Salt deprivation	Normal ^{96 146}
4 Balance	
a Nitrogen	Positive, at least during onset ^{1 1 17 131}
b Calcium	Positive or negative
c Phosphorus	Positive ^{1 133}

5 Vasomotor	Subnormal response
J BREASTS	
1 Male	Normal
2 Female	Normal or atrophy
K ABDOMEN	
1 Liver	Normal
2 Spleen	Normal
3 Hernia	None
4 Tumor	None
5 Ascites	May occur ^{27 28 59 103 161}
L GENITALIA	
1 Male	
a Penis	Normal
b Testes	Normal
c Prostate	Normal
2 Female	
a External	Normal (see hair)
b Internal	Normal
M NEUROMUSCULAR	
1 Muscles	Normal or may be weak and flabby, hypotonic
2 Gait	Normal, slow, tendency to waddle, clumsy (also hand movements)
3 Tremor	None
4 Paresthesias	Normal or may be present in hands and feet
5 Reflexes	Normal or hypoactive
6 Vibration sense	Decreased, probably due to impaired perception
N SPEECH	Slow, dull, hesitant

VII LABORATORY DATA

A URINE	
1 General	Normal, may have oliguria
2 Special chemical analyses	
a Sugar	Absent
b Albumin	Small amounts may be found
c Nitrogen	Normal or decreased ^{3 12 14 III}
d Creatine	Normal or decreased ^{11 1 6 141 142 154 166}
e Creatinine	Normal or decreased ^{14 154 166}
f Sodium	Normal retention during onset ^{14 17}
g Potassium	Normal retention during onset ¹⁷
h Calcium	Decreased ^{3 4 1 8 133}
i Phosphorus	Decreased ^{7 4 233}
j Chlorides	Normal or decreased ¹¹⁶
k Iodine	Decreased ⁸
B HEMATOLOGY	
1 Red blood cells	Normal or decreased more often (about 3 to 4 million) 16 37 66 71 8 89 97 106 116 117 119 124 159 primary anemia has been reported ^{13 53 100 115}
2 Hemoglobin	Normal or decreased (about 70%), rarely increased ^{3 III} 68 8 106
3 White blood cells	Normal or decreased ^{10 16 8 68 8 88 106}
4 Differential	Normal or may have increased basophils and eosinophils relative lymphocytosis ^{10 16 37 8 88 106}

II	EPIPHYSEAL STATUS (bone age)	Normal
C	LONG BONES	Normal
D	VERTEBRAE	Normal
E	BONE TEXTURE	Increased calcification or density ⁵
F	MISCELLANEOUS	
1	Chest	Majority of cases show some enlargement of cardiac shadow often due to fluid (see Fig 174)
2	Arteries	Often calcified

IX ETIOLOGY

A SPONTANEOUS MYXEDEMA

- 1 Cause not known
- 2 Atrophy of thyroid gland may be found

B THYROIDITIS

- 1 Types
 - a Nonspecific (see 20 \)
 - b Riedel (see 21 \I)
 - c Hashimoto (see 22 \I)
- 2 Cause unknown

C PITUITARY FACTOR (see 6)

- 1 Antecedent and relative thyroid hypofunction may develop before the onset of pituitary failure
- 2 Selective deficiency of pituitary thyrotropic hormone may be postulated

D SURGICAL—Myxedema may follow

- 1 Subtotal thyroidectomy for
 - a Hyperthyroidism
 - b Thyroiditis
 - c Nodular goiter which is the result of previous thyroid deficiency (see 15 \II B 1)
- 2 Total ablation of thyroid

E IRRADIATION — Hypothyroidism develops after

- 1 Roentgen therapy (often temporary)
- 2 Radioactive iodine

F GOITROGENIC AGENTS

- 1 Thiouracil
- 2 Propylthiouracil
- 3 Potassium thiocyanate (occasionally)

G IODINE—Ingestion may rarely produce myxedema (see Fig 157)^{6 7 17}

X PATHOLOGY

A GROSS

- 1 Thyroid (see 14 \X A Table 11)
 - a Size
 - (1) Normal
 - (2) Enlarged
 - (3) Small (atrophic)
 - (4) Thin

b Consistency

- (1) Firm
- (2) Like muscle

c Fibrous tissue increased

d Cysts or nodules may be found

e Cut section

- (1) Pale
- (2) Homogenous

2 Pituitary—size

- a Normal
- b Enlarged sometimes

3 Heart and blood vessels

a Cardiac muscle

- (1) Pale
- (2) Flabby
- (3) Friable
- (4) Pseudohypertrophy due to swelling of fibers

b Pericardium—serous effusion and/or transudate if congestive heart failure complicates picture

c Weight of heart may be increased due to edema or actual hypertrophy when associated with hypertension

d Aorta

- (1) Sclerosis increased
- (2) Cystic degeneration may occur³⁴
- (3) Spontaneous rupture rarely

e Other blood vessels (see Fig 176)

- (1) Arteriosclerosis frequent
- (2) Coronaries often involved

4 Liver¹¹

- a Edema
- b Sclerosis
- c Central necrosis

5 Spleen¹¹

- a Congested
- b Sclerotic

6 Bones—calcification increased

7 Muscles¹¹

- a Pale
- b Edematous

8 Serous cavities—fluid may accumulate in all in variable amounts¹

5 Renal	
a Phenolsulfonphthalein	Normal ⁹³
b Urea clearance	May be diminished ⁹
c Concentration	Normal, unless nephritis is an associated disease ⁹
6 ACTH	Eosinophils show a subnormal response ¹³⁰
E MISCELLANEOUS	
1 Basal metabolism rate	Low, rarely may be normal (see Chart 40)
2 Circulation time	Prolonged (arm to tongue 15 to 25 sec), minute volume decreased ^{30 108 147}
3 Sedimentation rate	Normal
4 Specific dynamic action of protein	Decreased
5 Gastric analysis	Hypochlorhydria and achlorhydria (gastroscopy may reveal atrophy) ^{51 90}
6 Electrocardiogram	Usually some change, low QRS complexes, low or flat T waves, may return to previous normal state with therapy (see Figs 173 and 177)
7 Blood volume	Decreased or increased ¹⁵¹
8 Spinal fluid protein	Increased ^{1 133}
9 Fecal excretion ¹³¹	
a Calcium	Normal or decreased
b Phosphorus	Normal or decreased
10 Electroencephalogram	Alpha rhythm decreased, about 6/sec ¹³³
11 Capillary permeability	Increased (fluorescein method) ^{90 108 109}
12 Carotin	May be present ^{3 37 1 7}
F URINARY HORMONE ASSAYS	
1 FSH	Negative, occasionally positive, may be increased (25 r u and over, exclusive of menopausal group) ^{7 88 40 69 90}
2 LH	No data
3 Estrogens	Normal
4 Pregnandiol	No data
5 17 ketosteroids	Very low, about 2 to 4 mg /24 hrs, may not increase with therapy in spontaneous myxedema ^{83 80 40 49 80 100}
a Androgens (capon test)	Very low ¹⁰⁰
6 11 oxysteroids	Very low ^{43 149}
7 Aschheim Zondek	Negative
8 TSH	Increased (in blood and urine) or absent (blood) ^{18 19 81 41 63 83 110 1 9 144}
G BIOPSY	
1 Endometrial	May show hyperestrinism (metropathia hemorrhagica)
2 Testicular	No data possibly retarded spermatogenesis
H VAGINAL SMEAR	Normal or hypoestrin effect
I SEMEN ANALYSIS	Normal or oligospermia ¹³⁴

VIII ROENTGENOGRAPHIC FINDINGS

A SKULL	
1 Cranial vault	Normal
2 Sella turcica	Normal or may be enlarged from aneurysm (see 2 XIV H 9 Fig 180)
3 Mandible	Normal
4 Sinuses	Normal
5 Teeth	Normal or decayed

2 Degree of deficiency necessary to produce myxedema

- a It is generally assumed that myxedema results from practically complete loss of thyroid function
- b Hypophysectomy does not produce typical myxedema indicating that the thyroid is capable of low degree of function independent of pituitary
- c Various degrees of clinical myxedema can be produced by increasing or decreasing the dose of desiccated thyroid given to an athyroidal person
- d The pathologic process which produces relative thyroid deficiency probably progresses in most instances to complete destruction of secreting tissue except in nodular goiter
- e Because of the above it may be assumed that thyroid deficiency usually means athyroidism except during the period of transition from normal to complete loss

B ALTERATIONS IN PHYSIOLOGIC CHEMISTRY

- 1 There is decreased excretion (urinary and fecal) of the following as a result of lowered metabolism due to deficient thyroid hormone
 - a Creatine
 - b Nitrogen
 - c Urea
 - d Calcium
 - e Phosphorus
 - f Iodine
- 2 Iodine function in the body is decreased for little or none is used in thyroid hormone synthesis but some must be retained in tissue fluids since there is a
 - a Reduction in¹³⁶
 - (1) Urinary excretion
 - (2) Muscle content
 - b Distress on the administration of desiccated thyroid³⁸
- 3 Sugar (blood) decreased due to lowered
 - a Liver function
 - b Intestinal absorption
- 4 Cholesterol (plasma) is increased
- 5 Protein in
 - a Spinal fluid is increased
 - b Exudates may occur in all serous cavities

C ALTERATIONS IN BODY ORGANS AND TISSUES

- 1 Liver function is decreased as reflected by hypercholesterolemia due to a backlog of undistributed ingested cholesterol which can be lowered by diet and without thyroid medication (see Chart 42)
- 2 Pituitary thyrotropin
 - a Hypersecretion of this hormone is the only known increased function of the body
 - b Cells producing it may be affected ultimately by the lack of thyroid hormone
- 3 Adrenals
 - a Less active if the decreased 17 ketosteroid output is an index of such a function (see 25 VII F5)
 - b Hypothyroid patients respond less to adrenalin and ACTH
- 4 The following activities are decreased
 - a Central as well as sympathetic nervous system
 - b Circulatory
 - c Hematopoietic for normocytic (common) or hypochromic anemia indicates the sluggishness of bone marrow response
 - d Gastro intestinal
- 5 Cellular functions
 - a Alteration of
 - (1) Membrane permeability
 - (2) Electrophysical reactions
 - b Intracellular fluid increased
 - c Laying down of extracellular substances of
 - (1) Water
 - (2) Mucin
 - d Reduction of (voluntary and involuntary)
 - (1) Muscular strength
 - (2) Irritability

XIII DIAGNOSIS

A GENERAL

- 1 Mental processes retarded
- 2 Cold sensitivity
- 3 Skin—dry
- 4 Pulse rate
 - a Normal
 - b Slow
- 5 Cholesterol (plasma)—elevated
- 6 Protein (serum)—increased
- 7 Iodine (total or plasma bound)—low

- 9 Kidney
 - a Normal
 - b Interstitial nephritis
- 10 Brain
 - a Variable findings
 - b Subarachnoid or choroid plexuses may show¹¹¹
 - (1) Edema
 - (2) Degeneration
- II Microscopic
 - 1 Thyroid
 - Tissue may be absent
 - b Fibrosis ibundant
 - c Lymphoid and plasma cell infiltration
 - d Follicles (see Fig 175)
 - (1) Absent almost entirely
 - (2) Few may be scattered
 - (3) Colloid found occasionally
 - (4) Lack an epithelial lining
 - (a) Partially
 - (b) Completely
 - e Hyperplasia
 - f Endemic goiter
 - g Fetal adenoma
 - 2 Pituitary⁸
 - a Eosinophils decreased
 - b Basophils increased
 - c Colloid material is excessive in the pars intermedia
 - 3 Skin^{11 131}
 - a Collagen and elastic fibers are widely separated
 - b Corium shows
 - (1) Edema
 - (2) Mucinouslike material
 - c Epidermis has
 - (1) Hyperkeratosis
 - (2) Irregular atrophy
 - d Layers have perivascular and lymphocytic infiltration
 - 4 Muscles¹¹¹
 - a Edema
 - b Fibrosis
 - c Lipochrome may be present
 - d Vacuolization
 - Poor striations
- 2 Hair
 - a Fine
 - b Coarse
 - c Brittle
 - d Scant, falls out easily
 - e Permanent wave does not take very well
- 3 Drug sensitivity, especially to
 - a Sedatives
 - b Narcotics
- 4 Hoarseness
- B NEUROMUSCULAR AND SENSORY
 - 1 Cold sensitivity
 - 2 Memory poor
 - 3 Mental sluggishness
 - 4 Sleepiness
 - 5 Deafness
 - 6 Joint pains
 - 7 Mu cle
 - a Stiffness
 - b Soreness
 - 8 Weakness
 - 9 Fatigue
 - 10 Vertigo (labyrinthine)
 - 11 Dizziness
 - 12 Convulsions¹¹³
- C CARDIOVASCULAR
 - 1 Angina of effort
 - 2 Dyspnea
 - 3 Edema
- D GASTRO INTESTINAL
 - 1 Bloating
 - 2 Distention
 - 3 Constipation
 - 4 Weight gain
 - 5 Anorexia
 - 6 Dysphagia
- I GENITO URINARY
 - 1 Menorrhagia
 - 2 Oligomenorrhea
 - 3 Amenorrhea
 - 4 Sterility
 - 5 Abortions
 - 6 Libido decreaa.ed
 - 7 Impotence

XI SYMPTOMATOLOGY

A GENERAL

- 1 Skin
 - a Dry
 - b Coarse
 - c Cool

XII PATHOLOGIC PHYSIOLOGY

A INTRODUCTION (see Chart 50, p 479)

- 1 Pathologic changes that take place in myxedema are due to a deficiency of thyroid hormone which apparently is a catalyst and affects the anabolic and the catabolic processes of all body cells

XVI TREATMENT

A MEDICATION

1 Desiccated thyroid (USP)

a Dosage	GR DAILY
(1) Initial	$\frac{1}{2}$
(2) After several weeks	1
(3) Final	$1\frac{1}{2}$ 2
(4) Maximal or optimal	2

b Caution

(1) An initial large dose may invoke status anginosus and should be avoided (see Fig 181)

(2) Overdosage may cause symptoms of hyperthyroidism (see 26 \II)

■ Cholesterol (plasma) and metabolic determinations are useful, but often optimal dose is learned by patient

2 Drug tolerance

a Sensitivity (marked) to

- (1) Morphine
- (2) Barbiturates

b Adrenalin responsiveness is decreased

B MANAGEMENT

1 Obesity—reduction diet should be advised rather than larger doses of thyroid

2 Anemia

a Primary—liver

b Secondary—iron

(1) Doubtful benefit if primarily due to myxedema

(2) Look for other causes if not corrected after 3 months of adequate thyroid treatment

3 Arthritis

a Analgesics

b Physiotherapy

c Orthopedic measures

C RESULTS

1 Cardiovascular system (see Fig 181)

a Angina pectoris may

(1) Disappear possibly, due to muscle change rather than to coronary arteries

(2) Become worse probably because of coronary insufficiency

b Coronary thrombosis or infarction may occur during therapy

c Congestive failure may

(1) Respond to desiccated thyroid alone (see Chart 44)

(2) Improve with removal of fluids suggesting mechanical embarrassment as an important factor

d Electrocardiogram

(1) Reversion to normal usually (see Fig 173)

(2) If due to an associated organic disease may not revert to normal especially if bundle branch block

e Cardiac size regresses to normal unless previous hypertrophy was present (see Figs 174 178)

2 General outcome (see Fig 182)

a Improvement in

(1) Body and mental sluggishness

(2) Hair growth unless too old

(3) Skin

(a) Texture

(b) Moisture

(4) Gastro intestinal complaints although this is not always striking

(5) Gonadal dysfunction

(6) Joint stiffness

b Urinary and blood changes

(1) Cholesterol (plasma) decreases to normal unless too high, i.e. over 600 mg % (see Chart 42)

(2) Protein reverts to normal

(3) Increase usually, in

(a) Creatinuria

(b) Iodine (blood and urine)

(c) Hemoglobin

(d) 17 ketosteroids

c Basal metabolic rate becomes normal

II COMPLICATIONS

1 If large or maintenance doses are given initially the following may develop

a Angina or status anginosus

b Coronary infarction

c Palpitation

d Dyspnea

e Apprehension

f Muscular or bone

(1) Pain

(2) Cramps

g Mental aberrations

h Acute psychosis

i Vertigo

j Weakness

k Sudoresis

- 8 Basal metabolic rate averages between minus 30 and minus 40 per cent on repeated tests

B SUMMARY

- 1 Every item of above may be within normal limits in a given case if any two are absent the diagnosis is unlikely
- 2 Satisfactory therapeutic response (except for *anginal symptoms*) on usual thyroid dosage (not over 2 gr a day)
- 3 If patient is taking thyroid
 - a Medication should be stopped
 - b Basal metabolic rate and cholesterol (plasma) are determined in 2 or 3 weeks
 - Definite clinical signs may not appear for 1 to 3 months⁷

XIV DIFFERENTIAL DIAGNOSIS

A OBESITY

- 1 This is not an important diagnostic sign of myxedema although patients may be
 - a Overweight—60 per cent
 - b Normal or underweight—40 per cent¹
- 2 Absence of
 - a Dry skin
 - b Nonpitting edema
 - c Hair changes
 - d Cold sensitivity
 - Mental retardation
- 3 Cholesterol (plasma)—normal
- 4 Iodine (blood)—normal

B HYPOMETABOLISM (as for obesity)^{1,2}

C CHRONIC FATIGUE (as for obesity)

D SENILITY (as for obesity)

E CHRONIC NEPHRITIS

- 1 Retinitis—uncommon in myxedema
- 2 Pitting edema—present
- 3 Albuminuria—excessive
- 4 Protein (serum)
 - Decreased (most unusual in myxedema)
 - b Reversal of albumin globulin ratio

F HYPOPITUITARISM OR SIMMONDS DISEASE

- 1 Skin is smooth (see 4 VI E 5 VI E)
- 2 Pubic and axillary hair are absent
- 3 Weight loss is common
- 4 Mental lethargy rarely found
- 5 Menorrhagia is absent
- 6 Cholesterol (plasma) averages are lower

- 7 Electrocardiogram is more frequently normal

- 8 Pituitary tumor may be present

G OTHER CONDITIONS

- 1 A variety of other clinical states may raise the question of myxedema, on the other hand, many of the changes found in hypothyroidism may suggest other entities, for example
 - Cushing's syndrome
 - b Angina pectoris
 - c Congestive heart failure
 - d Pernicious anemia
 - e Mental disorders
 - f Simple constipation
- 2 Hypercholesterolemia is often found in (see 14 VIII D 1, 103 III I 2)
 - a Diabetes mellitus (in acidosis)
 - b Some otherwise normal people
 - c Old age
 - d Some cases of coronary arteriosclerosis
 - e Nephrosis
 - f Common duct obstruction
 - g Xantheloma or xanthelasma

XV COMPLICATIONS SEQUELAE AND ASSOCIATED DISEASES

A CARDIAC COMPLICATIONS (see Charts 43 and 44 Figs 178 and 179)³⁰

- 1 Angina of effort may be due to
 - a Coronary sclerosis
 - b Anoxia possibly
 - c Cardiac muscle damage (see 20 V B 3)
- 2 Coronary infarction⁸
- 3 Congestive heart failure
- 4 Polyserous effusions are not solely due to congestion
- 5 Hypertension
- 6 Coincidental cardiovascular disease

B ASSOCIATED DISEASES

- 1 Hyperparathyroidism⁸
- 2 Diabetes^{8, 120}
 - a Association with hypothyroidism—rare
 - b If myxedematous condition is proved diabetes becomes worse and vice versa
- 3 Xanthoma tuberosum
- 4 Arteriosclerosis
- 5 Vitamin deficiencies
- 6 Pernicious anemia¹³ as 100 115

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E. SURGICAL

- 1 Indication—removal of adenomatous goiter when associated with myxedema
- 2 Preparation—thyroid should be given preoperatively to relieve myxedema
- 3 Results
 - a A striking reduction in size of goiter may occur
 - b Removal of a large, nodular and distended goiter might bring about a return of normal thyroid function

61 65 67

XVII PROGNOSIS

A. GENERAL

- 1 Without treatment—estimated life span is from 10 to 15 years

2 With treatment

- a Good outlook apparently
- b If coronary artery disease is present patient may actually be better with out treatment, although this cannot be proved

XVIII CAUSES OF DEATH

A. SUMMARY

- 1 Myxedematous coma, if not treated
- 2 Coronary
 - a Thrombosis
 - b Infarction
- 3 Status anginosus from overtreatment
- 4 Infections
- 5 Cerebral vascular accidents
- 6 Miscellaneous

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FIG 168 MYXEDEMA (*Left*) Classical myxedema (*Right*) Atypical appearance in myxedema Mentally sluggish Dry skin Plasma cholesterol 200 mg % BMR minus 20% Pulse 58 Administration of 1 gr desiccated thyroid Plasma cholesterol 200 mg % BMR \pm 0% Relief of symptoms (Hurxthal L M Myxedema The Cyclopedia of Medicine (Piersol) Philadelphia, Davis pp 119 131)



FIG 169 MYXEDEMA in a nonobese woman Note sparsity of hair on head (*Left*) Before treatment (*Right*) After 3 months of desiccated thyroid orally Observe change in facial expression regrowth of hair and loss of bloaty appearance

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FIG 172 MYXEDEMA Age 28 Chief complaints dyspnea for over a year and angina of effort BP 110/10 Vital capacity 2 300 cc Excess hair on face neck arms and chest was noted 1 year before Female escutcheon Weight 148 lbs Plasma cholesterol 416 mg % BMR minus 33% Age 29 Weight 129 lbs BP 110/80 Patient taking 12 gr of desiccated thyroid per week Hair decreased in amount 17 ketosteroids on treatment were 5.8 and 6.5 mg/24 hrs Angina of effort relieved (Left) Photo taken 1 month after beginning of treatment with desiccated thyroid (initial photograph was lost) (Right) Five months later Note loss of hair on edge of forehead under chin and between and around eyebrows



FIG 170 MYXEDEMATOUS SKIN



FIG 171 MYXEDEMA Loss of head hair in myxedema and regrowth with treatment by desiccated thyroid

CHART 41 MYXEDEMA Age 65 female Effect of low cholesterol diet on plasma cholesterol in myxedema with angina pectoris Thyroid could not be tolerated in $\frac{1}{4}$ gr daily doses and low cholesterol diet was tiresome No clinical improvement Hypertension

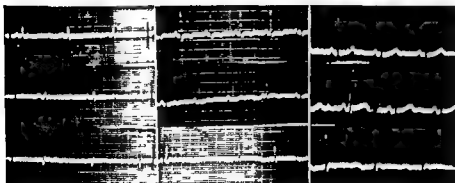
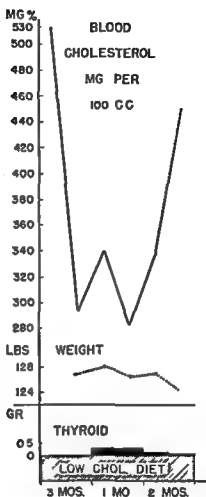


FIG 173 MYXEDEMA HEART WITH CONGESTIVE HEART FAILURE (See also Fig 178) Electrocardiograms taken before 10 days and 14 days after treatment Thyroxin given orally (Huxthal L M Myxedema heart with congestive heart failure and polyserous effusions New England J Med 213 264 267)

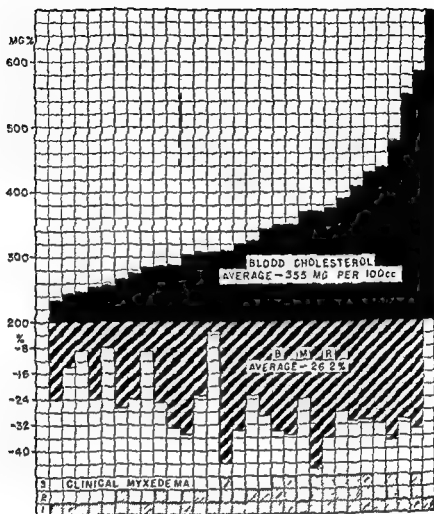


CHART 40 MYXEDEMA Variation in plasma cholesterol and BMR in 30 cases of spontaneous myxedema. Note that myxedema may be present with relatively little elevation of plasma cholesterol and occasionally with a normal BMR at least on first test. In the last case with the very high cholesterol only one BMR could be obtained. When myxedema was completely relieved plasma cholesterol was 300 mg % suggesting that myxedema was superimposed on an individual with idiopathic hypercholesterolemia. The shaded areas below depict the grade of myxedema as judged from physical findings (Hurxthal L. M. Blood cholesterol and thyroid disease III Myxedema and hypercholesterolemia Arch Int Med 53 762 781)

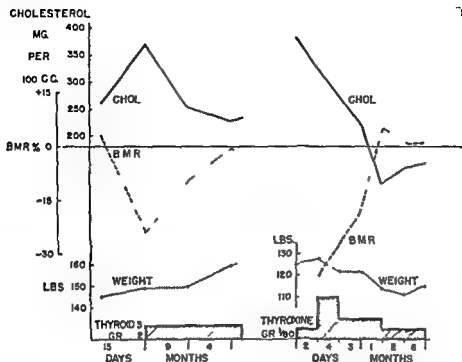


CHART 42 MYXEDEMA (Left) Age 45 female Effect of withdrawing desiccated thyroid on cholesterol BMR and weight in a patient with myxedema Physical changes may not become apparent for from 1 to 3 months (Right) Age 49 female Effect of administering thyroxine to a patient with myxedema in too large a dose Note gain in weight when thyroid was readministered (left) and inverse relationship between cholesterol and BMR The contour of the cholesterol curve is usually similar to contour of weight curve (Hurxthal L M Blood cholesterol and thyroid disease III Myxedema and hypercholesteremia Arch Int Med 53 /62 781)



FIG 177 MYXEDEMA Primary myxedema in a man of 24 complaining of fatigue Pulse was slow but no abnormality was noted in electrocardiogram



FIG 174 MYXEDEMA HEART Age 55 female Weight 144 lbs BP 100/80 Duration of symptoms 2 years RBC 3.9 million Hgb 10.6 Gm Hematocrit 33% Plasma cholesterol 362 mg % BMR minus 25% (Left) Heart before therapy (Right) Heart 2 months later Weight loss 9 lbs



FIG 175 MYXEDEMA Photomicrograph of thyroid gland in myxedema (See also Fig 176) Note scarring and small island of thyroid tissue remaining Follicular remnants are barely discernible Only a few of these were found on sectioning



FIG 176 MYXEDEMA Atheromatous residue almost completely filling the coronary artery in a man with myxedema dying of coronary failure The mass occluding the artery is filled with cholesterol Only a small portion of lumen remains The black areas are calcium deposits

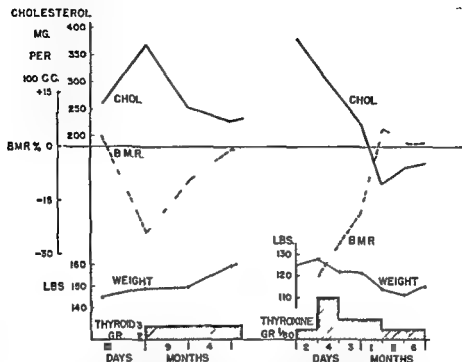


CHART 42 MYXEDEMA (*Left*) Age 45 female Effect of withdrawing desiccated thyroid on cholesterol BMR and weight in a patient with myxedema Physical changes may not become apparent for from 1 to 3 months (*Right*) Age 49 female Effect of administering thyroxine to a patient with myxedema in too large a dose Note gain in weight when thyroid was readministered (*left*) and inverse relationship between cholesterol and BMR The contour of the cholesterol curve is usually similar to contour of weight curve (Hurxthal L M Blood cholesterol and thyroid disease III Myxedema and hypercholesteremia Arch Int Med. 53 :62 781)



FIG 177 MYXEDEMA Primary myxedema in a man of 24 complaining of fatigue Pulse was slow but no abnormality was noted in electrocardiogram

CASES

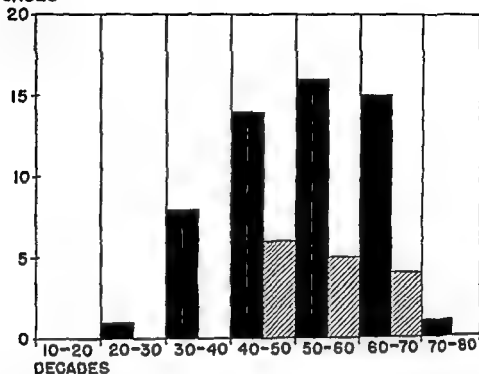


CHART 43 MYXEDEMA Age distribution in 59 cases of spontaneous myxedema (solid block) with cases manifesting evidence of coronary insufficiency i.e. angina of effort or coronary infarction (cross hatched) (Bartels E C and Bell G Myxedema and coronary sclerotic heart disease Tr Am A Study Goutier 1939 pp 5 15)



FIG 178 MYXEDEMA HEART WITH POLYSEROUS EFFUSIONS (See also Fig 173 and Chart 44) (Left) Before treatment (Right) Four weeks after treatment with thyroxin (Hurxthal L M Myxedema heart with congestive heart failure and polyserous effusions, New England J Med 213 264 267)

CHART 44 MYXEDEMA HEART (See also Figs 173-178) Myxedema heart with congestive heart failure and polyserous effusions. Treatment with bed rest and thyroxin 1/80 gr daily. Note diuresis as shown by loss of over 25 lbs. It was concluded that polyserous effusions were as much responsible for the pleural, pericardial and abdominal fluid as congestive failure (Hurxthal L M. Myxedema heart with congestive heart failure and polyserous effusions. *New England J Med* 213:264-267).

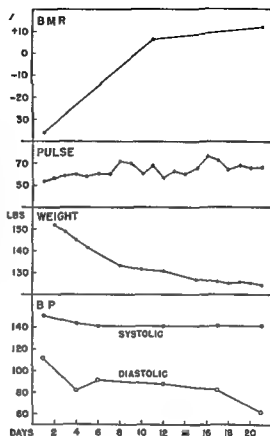


FIG 179 MYXEDEMA HEART (Left) Cardiac outline before pericardial tap (Right) After withdrawal of 450 cc of fluid. Note fluid level (arrow). (Freeman E B. Chronic pericardial effusion in myxedema. *Ann Int Med* 7:1070-1079).

CASES

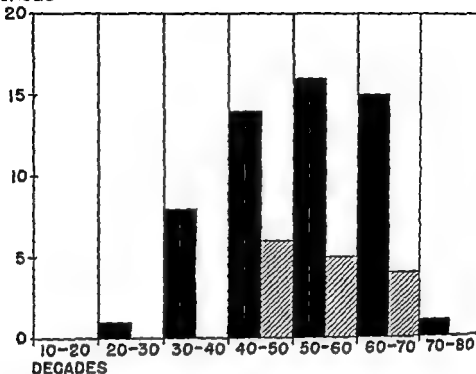


CHART 43 MYXEDEMA Age distribution in 59 cases of spontaneous myxedema (solid block) with cases manifesting evidence of coronary insufficiency, i.e. angina of effort or coronary infarction (cross hatched) (Bartels, E C and Bell G Myxedema and coronary sclerotic heart disease Tr Am A Study Gorter, 1939 pp 5 15)



FIG 178 MYXEDEMA HEART WITH POLYSEROUS EFFUSIONS (See also Fig 173 and Chart 44) (Left) Before treatment (Right) Four weeks after treatment with thyroxin (Hurxthal L M Myxedema heart with congestive heart failure and polyserous effusions New England J Med 213 264 267)

SECTION 26

HYPERTHYROIDISM

SYNONYMS

Hypersecretory diffuse hyperplastic goiter
Parry's disease
Graves's disease
Basedow's disease
Exophthalmic goiter
Primary hyperthyroidism
Thyrotoxicosis
Toxic hyperplastic goiter
Hypersecretory nodular goiter
Adenomatous goiter with hyperthyroidism
Nodular goiter with hyperthyroidism
Multiple colloid adenoma with hyperthyroidism

Toxic adenomatous goiter
Toxic nodular goiter
Hypersecretory solitary nodule
Hyperfunctioning adenoma
Hyperfunctioning solitary nodule
Toxic adenoma
Plummer's disease
Mixed types
Nodular or adenomatous goiter with superimposed Graves's disease or secondary hyperthyroidism nodular goiter and superimposed hyperplasia in remainder of gland
Hyperthyroidism with any coincident thyroid disease

I DEFINITION

Hyperthyroidism is characterized by an excessive production of thyroid hormone with subsequent increase in all metabolic processes and usually may be identified by the following the presence of goiter nervousness intolerance to heat excessive sweating weight loss (in spite of an adequate caloric intake) weakness fatigue tremor tachycardia an increased basal metabolic rate lowered plasma cholesterol an elevated blood iodine and creatinurea

II APPEARANCE

Normal alert or apathetic individual with a hunted expression or one of frozen fright when exophthalmos is present evidence of weight loss depending on severity and duration of the disease (see below Figs 183 187)

III AGE

A PRIMARY HYPERPLASTIC GOITER

Average 37 years (youngest $2\frac{1}{4}$ years oldest 81 years at Lahey Clinic)^{1,2,3}

B NODULAR GOITER

Average 49 years approximately

IV SEX

Females 88 per cent males 12 per cent

V MENTAL DEVIATIONS

A INTELLIGENCE

Normal or above average

B RESPONSIVENESS

Quick and alert

C OTHER ABNORMALITIES

Anxious emotional intense excitability depression psychosis or delirium may be present

VI PHYSICAL STATUS

A NUTRITION

Normal or poor

1 Weight

Variable more often decreased occasionally obese (see 26 VII C)

2 Fat distribution

Normal



FIG 180 PRIMARY MYXEDEMA Myxedema with aneurysm of internal carotid artery causing an enlarged sella. Age 65 BP 160/110 Plasma cholesterol 309 mg % Adrenal water test negative Urinary FSH strongly positive 17 ketosteroids 5.2 mg/24 hrs Typical physical signs of myxedema Improved with $\frac{1}{2}$ gr desiccated thyroid Angina of effort prevented larger doses It is believed that myxedema was primary and that the aneurysm was secondary in view of negative adrenal water test which is often positive when pituitary myxedema is present

FIG 181 MYXEDEMA Age 60 Previous adenomatous goiter removed surgically (Left) Condition after discontinuing thyroid for 1 year Rather severe angina of effort (Right) After 2 months of treatment with desiccated thyroid Given first in doses of $\frac{1}{4}$ gr a day and finally 1 gr a day There was no aggravation of angina in this case in fact some apparent improvement (Note regrowth of head hair)

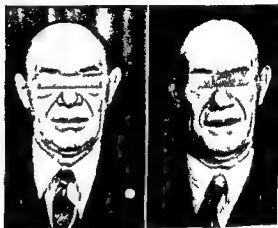


FIG 182 MYXEDEMA (Left) Age 47 Weight 203 lbs Plasma cholesterol 413 mg % Whole blood iodine 5.2 micrograms % BMR minus 36% (Center) After 3 weeks of treatment (Right) Age 49 Weight 165 lbs Plasma cholesterol 215 mg % Two gr of desiccated thyroid taken daily

3 Eyes (see Figs 190-193)

■ General

Normal or exophthalmos, unilateral or bilateral (25%), edema and/or tremor of the lids, blepharitis, excessive lacrimation, ulceration of the cornea, injected conjunctivae, icteric scleras (severe cases), may have paralysis of eye muscles especially the external recti or levator superior recti, photophobia. Exophthalmos of definite significance occurs in about 30 per cent of cases of diffuse hyperplastic goiter and in a few cases of hyperthyroidism with clinically nodular goiter presumably due to a superimposed Graves's disease. The authors have noted slight exophthalmos or lid retraction and stare in individuals taking large doses of desiccated thyroid. It is possible that excess thyroid secretion from a hyperfunctioning adenoma may produce a similar change.

b Signs

All few or none of these may be found

- (1) Dalrymple
- (2) Von Graefe
- (3) Stellwag
- (4) Jaffe
- (5) Moebius
- (6) Jellinek
- (7) Gifford
- (8) Sukers
- (9) Wilder

Widening of palpebral fissure

Lid lag

Stare or infrequent blinking

Forehead cannot be wrinkled

Lack of convergence

Pigmentation of eyelids

Difficulty in eversion of upper eyelid

Visual fixation from extreme lateral rotation

Jerking or twitching of globe when moving eye from extreme abduction to adduction

(10) Joffroy

Absence of brow wrinkling when looking upward and with the head down

(11) Rosenbach

Fibrillary tremor of closed eyelids

(12) Kocher

If looking upward at a moving object lids move in that direction but eyeballs do not (ophthalmoplegia)

c Fundi

Normal

d Visual

- (1) Fields
- (2) Acuity

Normal

Normal or impaired

4 Ears and nose

Normal

5 Mouth and throat

a General

Normal: tongue may be red, smooth, and occasionally has a tremor

b Teeth

Often carious: second teeth develop prematurely²⁰⁶

c Larynx (voice)

Normal

G NECK

1 General

Normal or fullness from the enlarged thyroid (see below); veins may be seen dilated and pulsating forcefully

2 Thyroid

Uniformly enlarged hyperplastic soft to firm, nodular or large single nodule (rare), thrills and bruits common (see 14 VIII D 2)

H CHEST

1 HEART AND PERIPHERAL VESSELS (see 30)

Normal: loss of intercostal flesh in severe cases

1 Heart

Normal or enlarged forceful apical thrust; systolic murmurs are frequent over pulmonic and apical areas; aortic diastolic murmurs are always due to an associated heart lesion; vital capacity reduced, holding of breath decreased²¹⁵

B HEIGHT	Normal or slightly taller than the average, if disease occurs before epiphyseal closure, ¹⁶¹ "thyroid gigantism" has been reported ¹⁶¹
C EXTREMITIES	Normal or evidence of weight loss, muscle atrophy and tremor
1 Upper	
a Hands	Normal size and shape, may have atrophy of thenar and hypothelar surfaces
b Fingers	Normal
c Span	Normal or increased
2 Lower	Normal or evidence of weight loss and muscular atrophy (see below)
a Feet	Normal deviations
b Toes	Normal
D SPINE	Normal, rounded or kyphotic from wedging of vertebrae in long standing cases with osteoporosis, especially in females
E INTEGUMENT	
1 General	
a Texture	Normal or fine, smooth
b Temperature	Warm to touch
c Moisture	Excessive sweating usually
d Eruptions	Uncommon
e Pigmentation	Tanning or bronzing may occur, partly from weight loss vitiligo more frequent (see Table 16 and Fig 188) ¹⁷⁸
f Color	Flushed appearance often, occasionally jaundiced redness of elbows from constant motion, marked dermatographia
g Nails	Fissures, nail bed concave or wavy, undergrooved, pigmented (see Fig 189) ³⁵¹
2 Hair	
a Head	Normal
b Facial	Normal
c Axillary	Normal or diminished ³⁵⁰
d Pubic	Normal or diminished
e Body	Normal males tend to be less hirsute than average ¹⁷⁹

TABLE 16 DIFFUSE PIGMENTATION
(BRONZING) AND VITILIGO³³

TYPE OF GOITER	NO OF CASES	NO OF CASES WITH PIGMENT	PER CENTAGE
Exophthalmic	293	42	14.3
Adenomatous without hyperthyroidism	371	2	0.5
Adenomatous with hyperthyroidism	26	4	15.3

F HEAD	Normal
1 Shape and size	Normal
2 Facial expression	Normal hunted or anxious when exophthalmos present appearance of "frozen fright"

2 Special chemical analyses	
a Sugar	Frequently (see 31)
b Albumin	Absent
c Nitrogen	Increased (see 26 VI) ^{129 371 379}
d Creatine	Normal or increased excess disappears after giving iodine ^{197 703 705 709 303 304 370 378 379 381 383}
e Creatinine	Normal or decreased ^{100 140 704 378 3 8 3.0 371 380}
f Sodium	Normal
g Potassium	Normal or increased
h Calcium	Increased ^{14 1 38 146 174 190 19 703 301 300}
i Phosphorus	Increased ^{14 39 149 301}
j Chloride	Normal or increased ³³
k Iodine	Increased may excrete from 40 to 950 gamma in urine daily depending on food iodine intake and blood level (see 103 IX C 3 c) ^{0 80 281 284}
l Diastase	Decreased ²²⁰
m Vitamin C	Decreased ¹⁴
n Urobilinogen	Present if liver damage
II HEMATOLOGY ^{100 23 776 300}	
1 Red blood cells	Normal ^{78 81 8 100 208 194 305} occasionally hyperchromic (incidence of pernicious anemia—1.9 % ³¹), hypochromic anemia ^{100 309} or polycythemia rarely ^{149 3 1 304}
2 Hemoglobin	Normal, may be reduced ^{100 184 312 300}
3 White blood cells	Variable ^{100 184 312 300}
4 Differential	Normal ^{79 8 113 100 106} monocytes increased occasionally relative or absolute increase in lymphocytes (not diagnostic) ⁴⁹ sometimes leukopenia, ^{78 80 106 31} iodine therapy produces no changes ¹⁸⁴ or only a decrease in monocytes ³³
5 Reticulocytes	Normal ³¹
6 Coagulation time	Normal or increased
7 Color index	Normal average ³¹
8 Bone marrow	Normal or myeloid hyperplasia ^{60 33}
9 Hemoconcentration	Normal ³³
C BLOOD CHEMICAL ANALYSES	
1 Sugar	Normal or increased slightly (see 31)
2 Nonprotein nitrogen	Normal (unless associated renal failure) ³³
3 Protein (see Chart 47)	Normal or decreased ^{-3 3 63 14 225 224 2 7 340}
a Albumin	Decreased (average per cent lower than normal)
b Globulin	Normal or increased
c Alpha globulin	Increased
d Other globulin fractions	No consistent change
e A/G ratio	Normal
f Fibrinogen	May be high
4 Uric acid	Normal
5 Cholesterol (plasma)	Usually decreased but may be normal or increased depending on previous level not especially helpful in diagnosis (see 14 VIII D 1) ^{37 175 176 223 3 4 840}
6 Sodium	Normal or decreased ^{133 224 370}
7 Potassium	Normal or increased ^{33 222}
8 Calcium	Normal may rarely be decreased or increased ^{14 39 146 177 179 44 281 783 301 300}

2	Rate and rhythm	Usually tachycardia and normal rhythm, auricular premature beats 3 to 4 per cent, ventricular extrasystoles are rare, paroxysmal auricular fibrillation preoperative or postoperative in from 10 to 20 per cent established auricular fibrillation in 5.8 per cent, all types of fibrillation 10 to 15 per cent ^{10 17 17}
3	Blood pressure	Variable (see Chart 52), pulse pressure increases with basal metabolic rate, paroxysmal or established true hypertension may be coexistent, percentage increase with age, ¹⁷³ usually some elevation of systolic and lowering of diastolic pressure, slapping sounds are heard as the level of diastolic pressure is approached (see 14 XIII B 6 b, Chart 46)
4	Peripheral arteries and veins	Forceful and collapsing radial pulse, easily compressed
5	Vasomotor	General cutaneous flushing, color "high"
J	BREASTS	
1	Male	Normal, gynecomastia sometimes ²²⁷
2	Female	Normal, occasionally atrophic and out of proportion to general weight loss
K	ABDOMEN	
1	Liver	Normal
2	Spleen	Frequently, but only slightly, enlarged
3	Hernia	Not present
4	Tumor	Not present
L	GENITALIA	
1	Male	
a	Penis	Normal
b	Testes	Normal
c	Prostate	Normal
2	Female	
a	External	Normal
b	Internal	Normal
M	NEUROMUSCULAR	
1	Muscles	Normal, atrophy or myasthenia ³⁸ positive quadriceps test (see 14 XIII B 5 b) atrophy of thenar and/or hypothenar eminences, weakness or paralysis of ocular muscles may occur, especially external or levator superior recti generalized hypotonia is common (see Fig 195)
2	Gait	Normal or slow if weakness of muscles exists
3	Tremor	Very fine, rapid quivering of hands may involve feet and whole body (often noted in roentgenograms or photographs)
4	Body movements	Not remarkable, other than tremulous
5	Paresthesias	Present rarely
6	Reflexes	Hyperactive usually
7	Vibratory sense	Normal or decreased
N	SPEECH	Rapid and lively, quick response

VII LABORATORY DATA

A	URINE	Normal
1	General	

- 6 Liver
 a Bromsulfalein
 b Hippuric acid
 c. Takata ara
- Poor efficiency has been demonstrated in severe cases
 Fifty per cent of cases have impaired excretion^{79 722 223 877}
 Normal or findings for variable degrees of damage^{23 24}
 32 76 129 173 317 330
 May be positive⁵
- E MISCELLANEOUS TESTS
 1 Basal metabolic rate
- Usually increased rarely normal⁷⁹ = 84 13 12 77

TABLE 17 RANGE OF METABOLIC RATES AND EFFECT OF IODINE¹⁸³

BMR RANGE (%)	ON ADMISSION		6 TO 10 DAYS LATER	
	No of Cases	Per cent of Total	No of Cases	Per cent of Total
-10 to +20	18	2.9	112	18.5
+21 to +50	212	34.9	363	60.0
+51 or over	377	62.1	132	21.8

Comment: Comparison of basal metabolic rates made on admission and 6 to 10 days later in those having both determinations. It will be noted that 62 per cent of patients had an initial basal metabolic rate of over 50 per cent whereas only 21.8 per cent had similar results 6 to 10 days after receiving iodine in some form.

- 2 Circulation time
 Decreased (arm to tongue) down to 6 secs, unless congestive heart failure in which case rate may be normal (see Chart 68) increased blood velocity and minute volume⁸³
- 3 Sedimentation rate
 Normal
- 4 Specific dynamic action of protein
 Variable²⁰⁰
- 5 Gastric analysis
 Increased number with achlorhydria^{46 6 84 09 100 103}
^{381 39} may be normal or increased (improvement with therapy)^{215 53 239 318}
- 6 Electrocardiogram
 Variable P and T waves may be high R low 'rolling' waves, any change may be present on account of coincidental heart disease (see Table 18)

TABLE 18 ELECTROCARDIOGRAPHIC CHANGES IN HYPERTHYROIDISM*

	PER CENT
Increased height of P waves	7-59
Delayed conduction	3-10
Abnormal T waves	3-22
Low isoelectric or negative T1	1-20
Low isoelectric or negative T2	8-10
High T waves	11-38
Extra systoles	1-14

* Adapted from summary of 22 reports in the literature by Hertz¹³⁸. It is not to be construed that the changes are all due to hyperthyroidism alone but rather to associated cardiovascular disease. The true incidence probably lies between the extremes.

- 7 Blood volume
 Increased³⁹
- 8 Spinal fluid proteins
 Decreased³⁵

9 Phosphorus	Normal or increased ¹ 35 146 190 281 283 301
10 Chlorides	Normal or increased ³³ 97
11 Phosphatase	Increased (especially in severe cases) ¹⁷ 194 199
12 Iodine	Increased (total and plasma bound) (see 103 IX C) ²⁷ 84 89 10 ² 181 217 218 228 270 271 281 9 287 31 333 363 387 391
13 Creatine	Normal or increased
14 Creatinine	Normal or decreased ³³ 100 2 9
15 Magnesium	Normal serum, but ultrafiltrable fraction is decreased and nonfiltrable (bound) fraction may be normal or increased ⁴³ 101
16 Lipids	Decreased (neutral fat normal), no relationship between height of cholesterol and level of neutral fat in serum ⁵ 47 53 253 273
17 Bilirubin	Normal or increased ¹¹ 22 223 307
18 Icteric index	Normal or increased (severe cases) ³⁷
19 Carbon dioxide combining power	Normal ³³ 36 83
20 Amylase	Decreased ³⁴
D FUNCTION TESTS	
1 Tolerance	
a Glucose	
(1) Oral	Normal or decreased (see Table 102) ⁷⁷ 1 3 15a 19 25 ² 203 316 387
(2) Intravenous	Decreased (see 103 I J 1 2) ⁷⁷
b Glucose insulin	No data insulin resistance reported ¹³⁴
c Insulin	Diminished (hypoglycemic unresponsiveness)
d Galactose	
(1) Oral	Rarely normal, elevated curve (normal after thyroidectomy) 3 20 23 216 221 224 305 319 344 349
(2) Intravenous	Normal or abnormal ²⁰ 20 341
e Iodine (see Chart 139)	Given iodine is removed quickly, no excess present in 6 hrs (average 2%), curve lower than normal ¹⁰ 22 300 373
f Creatine	Marked decrease i.e. 58 per cent (average) retention of amount ingested ¹⁹ 200 300 307 308 320 339 358 363
2 Adrenal water	Normal or positive ³³ 21
3 Salt deprivation	Normal or increased excretion of chlorides ³³ 211
4 Balance	
a Nitrogen	Usually negative but may be normal ⁵³ 54 63 100 109 10 2 4 not proportionate to level of basal metabolic rate can become positive on high protein intake and after successful therapy ¹⁸⁸
b Calcium	Variable 146 190 31 83 301 negative balance is unrelated to level of basal metabolic rate and may persist after subtotal thyroidectomy ¹⁴⁵ 146 may be related to nitrogen loss which is dependent not only on basal metabolic rate but the ingestion of protein food ²⁹⁴ until nitrogen balance is restored calcium is lost (see 26 XI A 2)
c Phosphorus	Negative or positive (see calcium balance) ¹⁴⁵ 146 253 301
d Potassium	Normal
e Iodine	Negative ⁷⁰ 81
5 Renal	
a Urea clearance	Normal

- b Shape (see Fig 196) Cardiac shadow like a ham because of slight auricular enlargement (auricular fibrillation), prominence of ven tricles and pulmonary arc dilatation may be present as well as increased hilar shadows in congestive failure
- Cardiac mensuration Size increased frequently,¹⁻⁴ after treatment may decrease or enlarge due to greater body weight i.e. postoperative myxedema or development of heart disease subsequently, superimposition of plates is desirable for comparison due to change in level of diaphragm with congestive failure (lowers it) and weight gain (raises it) (see Chart 45)
- 2 Stomach Normal delay in complete emptying time, increased prominence of gastric rugae, may have duodenal ulcer.^{83 151}
- 3 Intestinal tract Increased motility and tone⁶⁶ ■

IX ETIOLOGY

A HYPERSECRETORY HYPERPLASTIC THYROID

1 Unknown primary cause

2 Factors

a Heredity

- (1) Evidence suggests inheritance of a recessive characteristic favorable to its development^{60 233}
- (2) Identical or dissimilar twins may develop hyperthyroidism simultaneously.^{5 119 - 5}

b Two concepts regarding excess output of thyroid hormone

(1) Driving mechanism'

- (a) The thyroid gland is stimulated by an excess of pituitary thyrotropic hormone which results from some hypothalamic activity forcing unneeded thyroid hormone upon the body
- (b) The inhibiting effect of thyroid hormone is never sufficient to overcome the excess thyrotropic hormone otherwise the disorder would cure itself however this may be one explanation of spontaneous remissions (see 28 [I B 3])

(c) Inadequate iodine intake during stress and strain may contribute to initiating the cycle

(d) Emotional upheavals influencing brain and hypothalamus due to

(1) Strain (acute or chronic)

- [a] Physical
- [b] Worry
- [c] Grief
- [d] Fear
- [e] Shock

[2] Fever

[3] Starvation

[4] Weight loss in excess¹⁷⁴

[5] Hemorrhage

[6] Thyroid (desiccated) in large amounts¹⁷⁴

(2) 'Need mechanism'—the body tissues demand greater amounts of thyroid hormone because of a condition induced by primary unknown cause(s)

(a) Adrenals (alarm reaction of Selye) (see 99)

(b) Overproduction of pituitary specific metabolic hormone

(3) The circle of events is the same for both types but the starting point is different

(4) Hyperthyroidism in an acromegalic patient might be considered as an example of both mechanisms

B HYPERSECRETORY NODULAR GOITER

1 Cause obscure

2 Similar to other hypersecretory tumors

X PATHOLOGY

A Gross

1 Thyroid

a Symmetrical gland

9	Fecal excretion	
a	Calcium	High ¹⁴ 1 2 31 301
b	Phosphorus	Increased ¹⁴ 301
c	Iodine	Normal or increased ²⁸¹
d	Trypsin	Increased ¹⁷
■	Diastase	Increased ¹⁷
10	Electro encephalogram	Alpha rhythm increased ³¹⁰
F	URINARY HORMONE ASSAYS	
1	FSH	Negative, may be increased (exclusive of menopausal group) most show 24 ru or less, both males and females ¹¹ 170 171
2	LH	No data
3	Estrogens	Normal
4	Pregnandiol	No data
5	17 ketosteroids	Normal or slightly decreased, ²⁰ 109 11- 120 122 109 1 320 occasionally may show slight increase ¹⁰⁰ or decrease after iodine therapy ²³
a	Androgens (capon test)	Variable ¹⁰ 20
6	11 oxysteroids	Normal, ³⁰⁸ decreased ⁹ or increased ³ 0
7	Aschheim Zondek	Negative
8	TSH	Decreased or absent (active form) in urine (and blood), increased in the inactive form (see Chart 30) ⁷¹ 74 95 119 16 191 216 202 302 313
G	BIOPSY	
1	Endometrial	Variable
2	Testicular	Normal
H	VAGINAL SMEAR	Normal usually
I	SEMEN ANALYSIS	Normal probably

VIII ROENTGENOGRAPHIC FINDINGS

A	SKULL	
1	Cranial vault	Normal
2	Sella turcica	Normal
3	Mandible	Normal
4	Sinuses	Normal
5	Teeth	Carious frequently
B	EPiphySEAL STATUS (bone age)	During growth period may show accelerated union of epiphyses ⁴⁴ 69 20 377
C	LONG BONES	Increased longitudinal growth if hyperthyroidism occurs during growth period
D	VERTEBRAE	Normal ¹⁷⁸ or in longstanding cases osteoporosis occasionally with wedging of vertebrae
E	BONE TEXTURE	Normal except cases of long standing show osteoporosis ¹⁴
F	MISCELLANEOUS	
1	Heart and great vessels (see 30 VIII A)	
a	Fluoroscopy	If severe toxicity, forceful and violent heart beats and aortic pulsations, pulmonary arc is straight or convex in 43 per cent ¹⁷⁹ (may be demonstrated by indentation of esophagus on swallowing rugar), limited descent of diaphragm if congestive failure is present

- [a] Golgi apparatus
- [b] Mitochondria
- [3] Vacuoles increased
- [4] Colloid droplets at apex
- (b) Colloid decreased
- (c) Acini show
 - [1] Increase in size
 - [2] Papillary processes
- (d) Stroma contains
 - [1] Vessels which are
 - [a] Dilated
 - [b] Increased
 - [2] Abundant lymphatic tissue
 - [3] Fibrous tissue (late) which is
 - [a] Dense
 - [b] Thick
- (2) Multiple hypersecretory nodular goiter
 - (a) All types of nodules may be found
 - (b) Adenomas containing the following follicles are the most likely source of hormone
 - [1] Large
 - [2] Small
 - [3] Tubular
 - [4] Papillary
 - (c) Epithelium may be
 - [1] Hypertrophied
 - [2] Hyperplastic
 - (d) Uninvolved tissue may show
 - [1] Involution
 - [2] Colloid nodules
 - [3] Fibrosis
 - [a] Small bands
 - [b] Marked cirrhosis
- (3) Solitary hypersecretory nodule
 - (a) Nodule contains large and small follicular hyperplasia
 - (b) Uninvolved tissue shows involution
- b After treatment (see Figs 197 and 198)
 - (1) Diffuse hyperplasia
 - (a) Iodine—various degrees of involution
 - (b) Thiouracil—increase in hyperplasia
 - (c) Iodine and thiouracil—involution very often
 - (2) Hypersecretory nodules

- (a) Iodine—involution of peripheral cells of adenoma
- (b) Thiouracil—persistence of hyperplasia
- (c) Iodine and thiouracil—no data

2 Pituitary—see 2 IX B 15

XI PATHOLOGIC PHYSIOLOGY

A SUMMARY (see Charts 48 to 50)

- 1 The location of the initial disturbance is unknown
- 2 It may be the result of (see 88 VIII L)
 - a Stimuli from hypothalamus which
 - (1) Originate there
 - (2) Are conveyed from psychic disturbances
 - (3) Increase the amount of thyrotropic hormone, thus driving the thyroid gland excessively
 - b Some factor which creates a greater demand for thyroid hormone in the tissues thus drawing it out from the thyroid gland or via the pituitary as in the first instance
- 3 Evidence favors an excessive amount of thyroid hormone which causes
 - a Greater metabolic activity in all body cells
 - b Catabolism probably exceeds anabolism with few exceptions i.e. growing child
 - c A loss of
 - (1) Bone calcium
 - (2) Nitrogen
 - (3) Muscle protein
 - (4) Liver glycogen
 - d Depleted state
 - (1) When above processes continue unabated (i.e. excessive combustion) the patient may
 - (a) Literally burn himself up
 - (b) Die in delirium with hyperthermia
 - (2) Under these circumstances
 - (a) Histologic as well as physiologic changes occur in
 - [1] Muscles
 - [2] Liver
 - [3] Other organs
 - (b) Fat stores are used for fuel in an attempt to supply the lost protein
 - (c) Carbohydrate utilization may be inadequate

- (1) Size
 - (a) Normal occasionally
 - (b) Moderately enlarged (50 to 200 Gm)
- (2) Consistency—firm
- (3) Appearance
 - (a) Lobulated
 - (b) Meaty
 - (c) Beefy
- (4) Colloid content poor
- (5) Very vascular
- (6) Cut surface resembles pancreas
- b Nodular type
 - (1) Changes are due to recurring episodes of
 - (a) Hypertrophy
 - (b) Hyperplasia
 - (c) Involution
 - (2) Size and shape of gland and nodules show marked irregularity
 - (3) Consistency
 - (a) Firm
 - (b) Soft
 - (4) Appearance
 - (a) Meaty
 - (b) Translucent
 - (5) Degenerative areas
- 2 Pituitary—normal
- 3 Parathyroids
 - a Normal
 - b Adenoma occasionally found⁴⁵
- 4 Adrenals^{23 207}
 - a Normal
 - b Atrophy
 - c Hyperplasia
 - d Degenerative changes
- 5 Gonads—normal
- 6 Thymus—present in one half autopsied cases²¹⁵
- 7 Heart
 - a Size may parallel duration and degree of
 - (1) Hyperthyroidism
 - (2) Hypertension
 - (3) Other cardiac disease
 - b Dilatation with¹⁷⁷
 - (1) Auricular fibrillation
 - (2) Congestive heart failure
 - c Hypertrophy may be slight^{61 110 111 176 196 267 307}
 - d Associated pathology from other cardiac disease
 - e The so called brown atrophy has not been reported in recent years¹²⁰
- 8 Liver^{41 66 133 198 214 278 28 311 313 3 37}
 - a General
 - (1) Lesions may be
 - (a) Acute
 - (b) Chronic
 - (c) Combination of both
 - (2) Weight is less than normal in most cases
 - (3) Damaged in 50 per cent of cases
 - (4) Findings depend on the severity and duration of hyperthyroidism
 - b Types of changes
 - (1) Normal
 - (2) Acute degeneration
 - (a) Fatty metamorphosis
 - (b) Necrosis
 - [1] Central
 - [2] Focal
 - (3) Atrophy
 - (a) Simple
 - (b) Subacute
 - (4) Hepatitis (generalized)
 - (5) Cirrhosis²⁰⁰
 - (6) Chronic passive congestion
- 9 Spleen
 - a Normal
 - b Weight increased slightly
 - c Chronic passive congestion
- 10 Kidneys
 - a Normal
 - b Chronic vascular nephritis (associated condition)²¹⁴
- 11 Lymphoid tissue—generalized hyperplasia
- 12 Muscles
 - a Fatty degeneration may be present
 - b Atrophic changes
- 13 Skeleton
 - a Long bones
 - (1) Slender
 - (2) Cortices may be thin
 - b Osteoporosis of variable degrees
- 14 Exophthalmos (if present) (see 33 IV)
- B MICROSCOPIC (see 14 IV B 2 c, d)
 - 1 Thyroid
 - a Before treatment
 - (1) Diffuse hyperplasia
 - (a) Epithelium
 - [1] Columnar
 - [2] Increased size and number of

- 3 Tremor fine
 - 4 Pruritus
 - 5 Nervousness
 - 6 Emotional instability
 - 7 Psychoses
 - 8 Insomnia (uncommon)
 - 9 Fatigued easily
 - 10 Muscular weakness
 - 11 Bone pain (rare from osteoporosis¹³)
 - 12 Coma (infrequent)
- B CARDIOVASCULAR**
- 1 Tachycardia usually
 - 2 Palpitation
 - 3 Dyspnea on exertion
 - 4 Angina of effort
- C GASTRO INTESTINAL**
- 1 Weight
 - Loss
 - b Gain by some on account of excess appetite (3.5%)

TABLE 19 WEIGHT CHANGES IN
HYPERTHYROIDISM¹³

POUNDS	NO OF CASES
Weight lost	
1-10	174
11-20	249
21-30	187
31-40	107
41-50	55
51-60	31
61-70	18
Weight gained	28
No change	59
Not recorded	97
Total	1000

- 2 Appetite excellent but anorexia later in disease
 - 3 Thyroid crises (before or during)
 - a Diarrhea
 - b Nausea
 - c Vomiting
- D GENITO URINARY**
- 1 Amenorrhea
 - 2 Oligomenorrhea
 - 3 Frequency due to
 - a Nervousness
 - b Diabetes mellitus
- E MISCELLANEOUS**
- 1 Goiter
 - 2 Exophthalmos
 - a Unilateral
 - b Bilateral

XIII DIAGNOSIS (resume)

A HISTORY

- 1 Adequate caloric intake with simultaneous weight loss (in absence of diabetes)
- 2 Heat intolerance

B PHYSICAL STATUS

- 1 Skin has greater than normal
 - a Warmth
 - b Moisture
- 2 Eye signs (see 26 VI F 3 b)
 - a Exophthalmos
 - b Stare
 - c Lid retraction
- 3 Thyroid
 - a Visible prominence of gland
 - b Enlarged usually with rare exceptions
 - c Firmer than normal but not always
 - d Bruits in 70 per cent
- 4 Pulse rate and pressure are increased
- 5 Tremor is fine

C LABORATORY DATA

- 1 Cholesterol (plasma) is decreased but not diagnostic
- 2 Iodine (blood and urine) is increased
- 3 Basal metabolic rate may be
 - a Increased in majority
 - b Normal occasionally
- 4 Radioactive iodine—see 14 I V B 1 a and Tables 13 and 24

D COMMENT

- 1 There is no irreducible combination of the above which will invariably establish a diagnosis
- 2 Any one of the above signs or symptoms may be absent
- 3 If the following are all present, the diagnosis seems certain
 - a Weight loss with a proved adequate intake of food in the absence of diabetes mellitus
 - b Basal metabolic rate which is elevated
 - c Exophthalmos (measurable)
- 4 Therapeutic trial of iodine or antithyroid drugs results in
 - a Weight gain
 - b Pulse rate decrease
 - c Basal metabolic rate decline

4 Liver

- a Organic iodine compounds are ⁶¹
 - (1) Broken down
 - (2) Secreted into bile
 - (3) Reabsorbed (partly) by intestines, contributing further to thyroid intoxication

- b Function is reduced especially in severe hyperthyroidism, so that less hormone is destroyed

5 Cardiac changes

- a Histology of cardiac muscle is not characteristically altered ^{61 86 37}
- b The following substances are lost from cardiac muscle⁹¹

- (1) Glycogen
- (2) Creatine
- (3) Potassium
- (4) Phosphate

- c Hypertrophy of only a slight degree is found with coincidental heart disease

d Dilatation with

- (1) Auricular fibrillation is frequent with involvement of the auricles
- (2) Congestive failure is the same as in other cardiac diseases with decompensation without hyperthyroidism (see 27 VII)

- e Auricular fibrillation possibly results from

- (1) An increase in
 - (a) Thyroid hormone to cardiac muscle
 - (b) Epinephrine secretion³⁰⁷
 - (c) Metabolic rate
- (2) Auricular dilatation
- (3) Pre-existing heart disease, including degenerative cardiovascular changes

- f No conclusive proof exists that hyperthyroidism

- (1) Damages the heart although it may produce physiologic exhaustion
- (2) Associated with auricular fibrillation is evidence of structural abnormalities

6 Adrenals

- The low excretion of 17 ketosteroids suggests a depression of cortical function although cortin or 11 oxysteroid excretions are not consistently affected^{2 178 2 0}

- b Overactive in some cases possibly^{1 7}

- 7 Lymph glands and thymus may remain undiminished in size, suggesting an inability of the adrenal "S" hormones to operate and instigate the alarm reaction, which might overcome the frequent infections that cause death

- 8 Pulmonary infections are often suspected in thyroid crises but are seldom demonstrated convincingly at postmortem because purulent exudative lesions are not found

9 Creatinuria (see Chart 31)³⁵⁰

- a A result of disturbance in muscle metabolism due to the abnormal liberation of creatine by the thyroid hormone

- b It is associated with the muscular weakness and apparent dystrophy

- c Nature of this process is unknown but probably enzymic

10 Thyrotropic hormone concentration in

- a Urine²²

- (1) Active form—decreased
- (2) Inactive form (reactivated by certain reducing agents)—increased

- b Blood is decreased because of rapid inactivation by hypersecretory thyroid cells probably²²³

11 Iodine (blood and urine) is increased

- a Organic or protein bound iodine is the best index of circulating thyroid hormone

- b The thyroid eventually contains less iodine, and, unless the intake is increased the body loses its reserve

- c Later, the turnover of iodine becomes more rapid necessitating conservation

- (1) An enzyme ("iodase"²⁶⁹) capable of more rapid breakdown of organic iodides for absorption and reconversion into thyroid hormone apparently is produced²¹⁴

- (2) At such times the blood iodine is reduced to normal levels

XII SYMPTOMATOLOGY

A NEUROMUSCULAR AND SENSORY

- 1 Heat intolerance
- 2 Perspiration excessive usually

- 4 Lesion—may be demonstrated
- 5 Goiter—absent
- 6 Blood studies normal except for
 - a Anemia—secondary
 - b Sedimentation rate—increased
- 7 Basal metabolic rate—normal (in absence of fever or complications)
- 8 It is rarely associated with hyperthyroidism

F MALIGNANCY OF VARIOUS ORGANS

- 1 Progressive weight loss because of decreased caloric intake
- 2 Absence of
 - a Heat intolerance
 - b Nervousness (not marked, if present)
 - c Goiter
- 3 Localization of lesion may be possible
- 4 Iodine (blood)—normal
- 5 Basal metabolic rate
 - a Normal usually
 - b Variable

G AURICULAR FIBRILLATION WITH OR WITHOUT EVIDENT HEART DISEASE

- 1 Hyperthyroidism signs and symptoms are not found
- 2 Goiter absent usually may have non-toxic type
- 3 About 6 per cent of all patients with auricular fibrillation have hyperthyroidism but if statistics from large goiter clinics are included, the incidence is 16 per cent (from 4,647 cases collected from the literature by Aasstrup¹)

H PARKINSON'S DISEASE

- 1 Tremor
 - a Pill roll coarse
 - b Minimal or absent with voluntary movement
 - c Persistence at rest but stops during sleep
 - d Upper extremities commonly involved but entire body may be affected
- 2 Muscle rigidity
 - a Masklike facies
 - b Slow shuffling gait without arms swinging
 - c Festination
- 3 Sialorrhea

I FACTITIOUS HYPERTHYROIDISM (see 34 \I)

- 1 Eye signs—rarely
- 2 Thyroid enlargement—absent
- 3 Iodine (urinary) excretion—in excess

XV COMPLICATIONS SEQUELAE AND ASSOCIATED DISEASES

A COMPLICATIONS AND SEQUELAE

- 1 Acute thyroid crisis or thyroid storm (see 26 \VI \I)
- 2 Persistent hyperthyroidism (see 27)
- 3 Recurrent hyperthyroidism (see 28)
- 4 Myxedema (postoperative) (see 26 \VI \I 2 a)
- 5 Postoperative complications (see below)
- 6 Complications of antithyroid drugs (see 26 \VI D 5)
- 7 Acute congestive heart failure with thyroid crisis
- 8 Congestive heart failure without acute cardiovascular symptoms (see 30 \I)
- 9 Exophthalmos (malignant with severe lid involvement) (see 33 \I)
- 10 Malignant degeneration of thyroid gland^{123 235}
- 11 Liver damage²²⁵
- 12 Diabetes mellitus
- 13 Muscular dystrophy
- 14 Vitiligo

B ASSOCIATED DISEASES

- 1 Almost any disease may coexist with hyperthyroidism
- 2 Common
 - a Hypertension
 - b Rheumatic heart disease
 - c Diabetes mellitus
- 3 Rare
 - a Acromegaly (see 10 \V B)
 - b Hypoparathyroidism and hyperparathyroidism^{7 113 145}
 - c Addison's disease^{5 50 60 113 127 178}
 - d Eunuchoidism^{16 178}
 - e Pernicious anemia (19%)⁵¹
 - f Thrombocytopenic purpura⁷
 - g Familial periodic paralysis¹⁶⁷
 - h Myasthenia gravis^{31 81 200 210}
 - i Parkinson's disease
 - j Tuberculosis

E NODULAR GOITER WITH HYPERTHYROIDISM (see Fig 194)

- 1 Except in cases of a discrete hypersecretory adenoma,⁷⁸ it is difficult to separate nodular goiter from diffuse hyperplastic goiter on clinical grounds alone
- 2 In the early cases of hypersecretory diffuse hyperplastic goiter, the microscopic picture is characteristic, but in those cases of long standing the differentiation may be extremely difficult
- 3 Hypersecretory diffuse hyperplastic goiter may develop acutely upon a nodular gland, with or without exophthalmos
- 4 The development of hyperplastic goiter may be insidious and the same underlying cause may operate in a person with nodular goiter
- 5 The acute type of hyperthyroidism demands attention because of its severity, whereas the insidious type may exist years before the illness is recognized, causing the hyperplastic gland to become irregularly involuted and nodular

XIV DIFFERENTIAL DIAGNOSIS

A NEUROCIRCULATORY ASTHENIA (including tachycardia, anxiety neurosis and similar conditions)¹⁸⁰

- 1 Anorexia accounts for weight loss, if it has occurred
- 2 Hands are often
 - a Cold
 - b Clammy
- 3 Eye signs absent
- 4 Goiter
 - a None
 - b Colloid or nodular type may infrequently complicate picture
- 5 Pulse pressure is not increased, except under unusual emotion, especially in potential hypertension
- 6 Quadriceps test negative (see 14 VIII B 5 b)
 - a Patient gives up quickly
 - b No tremor of leg
- 7 Iodine (blood)—normal
- 8 Basal metabolic rate
 - a Normal usually
 - b Several tests may be necessary to establish trend (see 14 XIII D 3)
- 9 No response to Lugol's solution as a therapeutic test

B HYPERTENSION

- 1 Diastolic pressures are higher, except when both diseases coexist
- 2 Weight loss—unusual
- 3 Eyes
 - a Retinal changes more frequent
 - b Exophthalmos may be slight
 - c Other signs absent
- 4 Renal impairment—commoner
- 5 Iodine (blood)—may be elevated
- 6 Basal metabolic rate may be elevated in
 - a A patient with an adrenal medullary tumor
 - b Congestive heart failure
 - c Some cases without either (a b)¹⁰⁸

C DIABETES (see 31, 84 VIII)

- 1 Family history of disease
- 2 Weight loss—common
- 3 Absence of
 - a Heat intolerance
 - b Tremor
 - c Diarrhea
 - d Tachycardia, except with
 - (1) Acidosis
 - (2) Coma
 - e Palpitation
 - f Sweating excessively
- 4 Goiter—absent
- 5 Sugar (blood)—elevated
- 6 Iodine (blood)
 - a Normal
 - b Increased
- 7 Basal metabolic rate
 - a Normal usually
 - b Increased occasionally

D ACROMEGALY

- 1 Headache is very frequent complaint, but rare in hyperthyroidism
- 2 Early in disease there is very little increase (later quite evident) in size of
 - a Facial features
 - b Hands
 - c Feet
- 3 Visual field changes may be found about 20 per cent¹⁷⁸
- 4 Sella turcica is enlarged (over 95%)
- 5 Hyperthyroidism is often an integral part of acromegaly (see 10 V B XVI E 1)

E PULMONARY TUBERCULOSIS

- 1 Anorexia—more common
- 2 Nervousness—less evident
- 3 Fever—usually

TABLE 20 SUMMARY OF EFFECTS ON RETURN OF NORMAL THYROID FUNCTION

	7 TO 14 DAYS	90 DAYS
BMR	Normal	Normal
Pulse (unless auricular fibrillation)	Normal	Normal
Weight	Little or no change	15 to 17 lbs average gain
Cholesterol	Slight rise	Return to values present before onset
Blood pressure		
Systolic	Lower	Lower
Diastolic	Higher	Higher
Blood iodine		
Whole blood (total)	Normal (unless on iodine)	Normal
Plasma protein bound	Normal (unless on iodine)	Normal

mission occurs but if it rises, a natural relapse is taking place

- d If the basal metabolic rate is normal before operation as the result of treatment then the usual changes found in 7 to 14 days after surgery have already taken place

- e Hypertension—except for changes as above course unaltered

- f Cardiac effects—see 30 XIV Charts 52 and 53

- g Exophthalmos

- (1) Unless actual measurements are obtained with the exophthalmometer the true incidence of recession of the eyeball cannot be accurately determined

- (2) On appearance alone a decrease in exophthalmos has been variously reported from 25 to 50 per cent

- (3) In 60 cases measured preoperatively and 100 days postoperatively, the following figures were obtained despite the fact that in many instances there was no noticeable improvement in the appearance of the eyes probably due to less lid retraction (see Fig 207 p 494) ¹

- (4) Actual measurements—see Table 21

- D ANTITHYROID DRUGS (see 14 VI G & B 1 d and Charts 54 and 55 for mode of action)

- 1 Indications—hyperthyroidism that is

- a Mild and without a large gland
b Recurrent
c Persistent

TABLE 21 MEASUREMENT OF EXOPHTHALMOS³³⁴

	NO OF CASES	PER CENT
<i>Initial Examination</i>		
Slight degree	26	
Significant	10	60
No change	24	40
<i>After Operation (100 Days Later)</i>		
Decrease		
/ mm or less	14	23.3
/ to 1 mm	4	6.7
Increase		
1 to 2½ mm	31	51.6
2½ mm or more	11	18.3

- 2 Disadvantages

- a Careful regulation of dosage is necessary for prolonged time
- b Partial control of hypersecretory nodular goiter may be serious in
- (1) Older age group
- (2) Psychotic patients
- (3) Associated heart disease
- c Persistence of goiter (cosmetic)
- d Permanent cure is unlikely and not recommended unless surgery is
- (1) Refused
- (2) Inadvisable
- e Remote dangers in nonsurgical treatment of multiple nodular goiters
- (1) Malignant change in less than 2 per cent (see Table 43, p 537) ³⁸
- (2) Tracheal deviation and compression may develop

XVI TREATMENT

A INTRODUCTION

- 1 The choice of treatment for hyperthyroidism is dependent on several factors
 - a Type of goiter
 - b Severity and duration of the disease
 - c Accessibility of a physician
 - d Desire or conviction of the patient or physician as to the necessity for surgery
- 2 Several methods of treatment are commonly used others have been tried with less favorable acceptance, these will be mentioned but not recommended
- 3 The best procedure for the present may be combined preparation with antithyroid drugs and iodine followed by subtotal thyroidectomy
- 4 Diffuse hyperplastic and nodular goiters with hyperthyroidism are discussed together

✓B LUGOL'S SOLUTION (or capsules *)

- 1 Indications
 - a This method may be advisable in very mild cases with
 - (1) Basal metabolic rates under plus 25 per cent
 - (2) Little weight loss
 - (3) Diffuse hyperplastic goiter
 - b Therapeutic test—symptoms may be relieved, but may return when medication is discontinued
- 2 Dosage, oral—10 minims tid pc in chocolate milk
- 3 Complication—iodism
 - a Symptoms
 - (1) Rash
 - (2) Nose and eyes are watery
 - (3) Fever
 - b Therapy—discontinue medication
 - c Substitute
 - (1) Amend's solution
 - (2) Diiodotyrosine
- 4 Results
 - a Basal metabolic rate may return to normal
 - b All symptoms may be relieved as long as medication is taken
 - c Underlying cause may persist and/or increase so these patients should then be treated with

(1) Antithyroid drugs first

(2) Subtotal thyroidectomy later

d Refractoriness to iodine may be attributed to

- (1) Previous and recent intake of this drug
- (2) Sudden exacerbation of disease neutralizing the effects of iodine
- (3) Failure to take medication
- (4) Self induced (factitious) hyperthyroidism
- (5) Unrecognized acromegaly
- (6) Wrong diagnosis

✓ Diiodotyrosine and potassium iodide produce about the same results, although the first of these has been reported to act more quickly.^{1,2}

C IODINE PREPARATION FOLLOWED BY SUBTOTAL THYROIDECTOMY

1 Indications

- a This procedure may still be used safely without antecedent preparation by antithyroid drugs
 - b In view of the possibility of unpredictable severe postoperative reactions, surgery should not be undertaken unless there has been an excellent response with normal pulse and basal metabolic rate
 - c While the danger is remote, there is no point in risking a severe postoperative storm when antithyroid drugs are available
 - d The method is therefore not recommended any longer
- 2 Dosage—as above B 2
 - 3 Results—summary of principal effects noted on return of normal thyroid function
 - a Certain changes develop after any form of therapy which reduces output of thyroid hormone to normal levels except in point of time
 - b If iodine brings basal metabolic rate to normal it will do so within 10 to 14 days whereas, thiouracil preparations require a longer time depending on height of basal metabolic rate
 - c If the basal metabolic rate continues to fall after 10 to 14 days on iodine it may be said that a 'natural re

TABLE 20 SUMMARY OF EFFECTS ON RETURN OF NORMAL THYROID FUNCTION

	7 to 14 Days	90 Days
BMR	Normal	Normal
Pulse (unless auricular fibrillation)	Normal	Normal
Weight	Little or no change	15 to 17 lbs average gain
Cholesterol	Slight rise	Return to values present before onset
Blood pressure		
Systolic	Lower	Lower
Diastolic	Higher	Higher
Blood iodine		
Whole blood (total)	Normal (unless on iodine)	Normal
Plasma protein bound	Normal (unless on iodine)	Normal

mission' occurs but if it rises a natural relapse is taking place

d If the basal metabolic rate is normal before operation as the result of treatment, then the usual changes found in 7 to 14 days after surgery have already taken place

e Hypertension—except for changes as above course unaltered

f Cardiac effects—see 30 \IV Charts 52 and 53

g Exophthalmos

(1) Unless actual measurements are obtained with the exophthalmometer, the true incidence of recession of the eyeball cannot be accurately determined

(2) On appearance alone a decrease in exophthalmos has been variously reported from 25 to 50 per cent

(3) In 60 cases measured preoperatively and 100 days postoperatively, the following figures were obtained despite the fact that in many instances there was no noticeable improvement in the appearance of the eyes probably due to less lid retraction (see Fig 207 p 494)²¹

(4) Actual measurements — see Table 21

D ANTITHYROID DRUGS (see 14 VI G \ B 1 d and Charts 54 and 55 for mode of action)

1 Indications—hyperthyroidism that is

a Mild and without a large gland

b Recurrent

c Persistent

TABLE 21 MEASUREMENT OF EXOPHTHALMOS^{33,4}

	NO OF CASES	PER CENT
<i>Initial Examination</i>		
Slight degree	26	80
Significant	10	
No change	24	40
<i>After Operation (100 Days Later)</i>		
Decrease		
$\frac{3}{8}$ mm or less	14	23.3
$\frac{1}{2}$ to 1 mm	4	6.7
Increase		
1 to 2 $\frac{1}{8}$ mm	31	51.6
2 $\frac{1}{8}$ mm or more	11	18.3

2 Disadvantages

a Careful regulation of dosage is necessary for prolonged time

b Partial control of hypersecretory nodular goiter may be serious in

(1) Older age group

(2) Psychotic patients

(3) Associated heart disease

c Persistence of goiter (cosmetic)

d Permanent cure is unlikely and not recommended unless surgery is

(1) Refused

(2) Inadvisable

e Remote dangers in nonsurgical treatment of multiple nodular goiters

(1) Malignant change in less than 2 per cent (see Table 43 p 537)²⁸⁸

(2) Tracheal deviation and compression may develop

f Histopathologic changes in thyroid gland have been considered as malignant

g Reactions to medication

✓3 Dosage (occasionally larger amounts of all preparations may be employed than given below)—administered orally

a Propylthiouracil

acid 0.3 to 0.4 Gm daily in divided doses (2 tablets of 50 mg each taken b i d or t i d)

b Thiouracil

(1) Initial 0.4 to 0.6 Gm daily

(2) Maintenance 0.1 to 0.2 Gm daily

c Thiobarbital (no longer available)

10 90 20 30 80

(1) Initial 0.05 Gm (50 mg) daily

(2) Maintenance 0.0025 Gm (25 mg) daily

d Methylthiouracil

acid 0.3 Gm daily²⁸ ³⁰⁰

✓ 1 Methyl 2 mercaptoimidazole

0.003 Gm (30 mg) daily³⁴

4 Management

a Continue with medication until basal metabolic rate is normal

b Reduce dose 75 per cent to maintain normal state for 6 to 12 months

c Watch for recurrence of hyperthyroidism

(1) Immediately

(2) In 3 to 4 weeks

(3) After 3 months

d Advise patient to note any signs and symptoms listed below

e Check white blood count and differential

(1) Thiouracil—every 2 weeks

(2) Propylthiouracil and methylthiouracil—once a month

5 Toxic effects—symptoms blood changes and physical manifestations (see Charts 56 and 57)^{68 88 12 43 80 104}

1 1 120 132 137 168 81 8 10 223 33 39
241 243 244 296 298 303 3 4 360 366 38 387

a Onset—usually like a mild upper respiratory infection

b General

(1) Psychosis

(2) Chilliness

(3) Fever

(4) Hyperhidrosis

(5) Skin changes

(a) Urticaria

(b) Rash

(6) Alopecia

(7) Pruritus

(8) Lymphadenopathy

(9) Exophthalmos may increase

c Neuromuscular

(1) Headache

(2) Malaise

(3) Aching joints

d Gastrointestinal

(1) Anorexia

(2) Nausea

(3) Vomiting

(4) Diarrhea

(5) Jaundice

(6) Polydipsia

(7) Mouth dryness

e Genito urinary—hematuria

f Hematologic

(1) Leukopenia

(2) Aggranulocytosis

(3) Thrombocytopenia

(4) Anemia

(5) Purpura

6 Treatment of complications

a Antithyroid preparation discontinued

b Penicillin immediately

(1) Intravenous

(2) Intramuscular

(3) Local throat spray

TABLE 22 TOXICITY OF ANTITHYROID DRUGS (LAHEY CLINIC)³⁰

	NO OF CASES	% OF TOTAL REACTIONS	% OF AGRANULOCYTOSIS
Propylthiouracil	1 273	2.3	0.7
Thiouracil	400	10	1.3
Methylthiouracil	99	13	1.0
1 Methyl 2 mercaptoimidazole	50	0	0
Thiobarbital	28	28	7.1

- c Supportive measures
 - (1) Fluids
 - (2) Oxygen if needed
 - (3) Sedation
 - (4) Transfusions if indicated
- d Subsequent therapy—another thiouracil preparation may be used without toxic effects⁹⁸
- 7 Results
 - a Subjective symptoms disappear first
 - b Weight increases as basal metabolic rate approaches normal
 - c Cardiac changes
 - (1) Dyspnea decreases
 - (2) Tachycardia responds
 - (3) Auricular fibrillation may revert to normal rhythm
 - (4) Congestive failure may improve
 - d Exophthalmos is not altered, except very rarely¹⁷⁸
 - e Bone marrow remains normal except with³⁰³
 - (1) Leukopenia
 - (2) Agranulocytosis
 - f Diabetes may or may not be affected²⁹⁷
 - g Urinary excretion
 - (1) Creatine—decreases
 - (2) Creatinine—increases
 - h Blood chemical analyses
 - (1) Globulin (serum)—increases
 - (2) Cholesterol (plasma)—increases
 - (3) Iodine (blood)—returns to normal
 - i Electrocardiogram may change as in myxedematous patients^{5 6}
 - j Final outcome has been⁶

11	1	—	27
40	4	90	10
106	1	1	123
1	4	20	38
701	204	06	708
204	2	4	374
333	333	334	
398	399		

 - (1) Variable
 - (2) Difficult to evaluate at present time
 - k Patients treated 6 months or more have a remission, in approximately 25 to 50 per cent of cases, for 1 year or more
- E ANITHYROID DRUGS FOLLOWED BY IODINE AND SURGERY
 - 1 Indication—all cases except very severe hyperthyroidism (see below)
 - 2 Dosage
 - a Antithyroid drugs
 - (1) Oral—see above
 - (2) Duration of therapy
 - (a) Diffuse hyperplastic gland
 - [1] Effective dosage—300 mg daily, but may require 400 mg
 - [2] Therapy continued until basal metabolic rate is normal
 - [3] Medication stopped when iodine is given (see below)
 - [4] Response—basal metabolic rate will drop on average of one point (of per cent elevation) per day (BMR plus 40% will require 40 days of treatment)
 - (b) Nodular gland
 - [1] Effective dosage—300 mg daily, but may require 400 mg
 - [2] Medication continued until basal metabolic rate is normal
 - [3] Operation is then performed
 - [4] Response—basal metabolic rate will drop average of one point (of per cent elevation) in every 2 days
 - (3) Morphine should be used with caution for these patients are very sensitive to it
 - b Lugol's solution
 - (1) Oral—10 minims tid pc in chocolate milk
 - (2) Time of administration
 - (a) Begun when basal metabolic rate is nearly normal
 - (b) Continued for 7 to 10 days before surgery
 - (3) NOTE—not necessary in nodular goiter but probably advisable
 - c Subtotal thyroidectomy (see 26 XVI L 2)—anesthetic course is excellent (see Chart 59)
 - 3 Results—essentially as for antithyroid drugs (see Tables 22 and 23, 26 XVI D 7)

TABLE 23 CHANGES IN BASAL METABOLIC RATE AND PLASMA CHOLESTEROL ON ADMINISTERING THIOURACIL (28 CASES)

	BMR (%)		PLASMA CHOLESTEROL (MG %)	
	Range	Average	Range	Average
Initial	+26 to +95	+56.3	120 to 215	165
Final	+19 to +27	- 4	144 to 404	228

F IODINE AND ANTITHYROID DRUGS TAKEN SIMULTANEOUSLY BEFORE SURGERY

1 Indications

- This method is recommended for severely toxic cases, both agents being administered simultaneously from the beginning¹
- Because of the relatively prompt action of iodine as compared with the slow action of antithyroid drug, thyroid crisis may be prevented in some cases before the latter becomes effective

2 Dosage—as above

3 Results—as above (D 7), but it may take longer to bring basal metabolic rate to normal because of the interference of iodine with the action of antithyroid drugs (see Chart 58)

G ROENTGEN^{103 135 23 18 74 77 323 341}

1 Over thyroid gland

a Indications

- When surgery is
 - Contraindicated
 - Refused
- If drug therapy is not tolerated
- Persistent hyperthyroidism
- Recurrent cases

b Method¹⁴⁷

- Thyroid gland just covered by a portal so that all portions receive approximately the same amount of rays
- Six treatments are given in each series, usually 3 series or more are necessary
- Factors
 - K V P 200 milliamperes 20 distance 50 cm
 - Daily dose 300 r
- After 2 months this may be repeated if there has not been a complete cessation in the clinical

evidence of hyperthyroidism

c Complications (none serious, unless thyroid crisis ensues before effect of therapy)

- Redness of the skin because more sensitive than normal
- Sore throat
- Tracheitis
- Esophagitis

d Results

- Thyroid gland may decrease in size
- Clinical condition generally satisfactory
- Severe cases have temporary benefit
- Myxedema may be produced only to be followed by return of thyroid activity in some
- Basal metabolic rate may be
 - Normal
 - Decreased

2 Over pituitary^{3,2 3,3}

a Indication—experimental

b Dosage—see 13 IV

c Results

- Pituitary and surrounding tissues might be damaged
- Percentage of cures is low
- Permanent remission reported in approximately one third of 43 patients

H RADIOACTIVE IODINE¹⁰³

1 Formation

- a Fourteen radioactive isotopes of iodine are known and 4 have been used biologically

	HALF LIFE
(1) I ¹²³	25 min
(2) I ¹³⁰	12 6 hrs
(3) I ¹³¹	13 0 days
(4) I ¹³¹	8 0 days

b I¹³¹ is used almost exclusively at present

- Production by bombarding tellurium¹³⁰ with slow neutrons in the chain reacting pile
- Available at approximately \$100 per millicurie from the Atomic Energy Commission Clinton Laboratories Oak Ridge Tenn

- (3) Ease of administration—given as a colorless and tasteless drink of water (Some samples may contain enough tellurium to produce garlic odor on breath of patient)
- 2 Action—radioiodine¹³¹ disintegrates to inert and harmless xenon each particle emitting a beta particle and two gamma radiations
- a Beta particles have
- (1) Maximal energy of 0.595 Mev (million electron volts)
 - (2) Average energy of 0.205 Mev
- b Gamma rays have a maximal energy of 0.360 Mev
- c Radiiodine acts physiologically and chemically the same as the stable isotope I^{127} except for the radiation effects
- 3 Indications
- a Radiiodine therapy should be limited to older patients until further clinical experience favors or disproves the fear of radiation injury^{107 7}
- b Williams lists the following indications in hyperthyroidism³⁰⁷
- (1) Poor surgical risks
 - (2) Patients who refuse surgery
 - (3) Postoperative recurrence of hyperthyroidism
 - (4) Vocal cord paralysis
 - (5) Sensitivity refractoriness or lack of co-operation in taking antithyroid drugs
- c Treatment of
- (1) Euthyroid cardiac patients by producing myxedema (experimental)⁴⁹
 - (2) Thyroid cancer
- 4 Dosage
- a Factors reducing thyroid uptake of radioiodine
- (1) Previous iodine therapy^{1,20 104 105}
 - (2) Propylthiouracil⁹⁴
 - (3) Thiocyanate²⁹⁰
 - (4) Reduction in the metabolic rate by exposure to warmth⁹⁰³
 - (5) Desiccated thyroid administration³³³
- b Total amount of iodide administered should be less than 2 mg ($\frac{3}{4}$ drop Lugol's solution)
- c Absorption in gastro intestinal tract
- (1) Radioiodine can be detected in human hand within 3 to 6 min¹⁴⁰
 - (2) Absorption complete in 3 hrs (food delays absorption)¹⁴³
 - (3) Fecal excretion is not more than 3 per cent¹⁴³
- d Deposition of radioiodine in thyroid (see Tables 15 and 24)^{141 144 106}
- (1) Thyroid can concentrate iodine to 10 000 times the blood level
 - (2) Uptake in
- | | PER CENT OF DOSE |
|--|------------------|
| (a) Normal thyroid | 15-30 |
| (b) Diffuse toxic or nodular goiter with hyperthyroidism | 40-85 |
- e Urinary excretion
- (1) Large part found in 48 hrs
 - (a) Normal 50-75
 - (b) Hyperthyroidism 5-50 - (2) The amount found within 72 hrs furnishes an accurate index of the percentage of the dose that will be collected by the thyroid
 - (3) Other body tissues probably take up about 10 to 15 per cent of the radioactive iodine
- f Calculation of radiation dosage
- (1) Bases for calculation
 - (a) Known empiric initial concentration of C microcuries per Gm of thyroid tissue (see Table 24)
 - (b) Clinical estimation of the thyroid gland weight
 - (c) Tracer dose I^{131} of 100 to 150 microcuries of carrier free radioiodine
- [1] Utilizing a Geiger counter in a fixed position over the thyroid gland determine the
 - [a] Fractional uptake of thyroid
 - [b] Accumulation gradient

TABLE 24 RESULTS OF TREATMENT OF HYPERTHYROIDISM WITH RADIOACTIVE IODINE

AUTHORS	CASES	ISOTOPE	MICROCURI-ES /1 GM OF THYROID	TOTAL DOSE mc	RESULTS (No Cases)			
					Good	Fair	Poor	Myxedema
Hertz and Roberts ¹⁶³	79	¹³¹ I ¹³¹ I		0.7- 11	20		9	
Chapman and Evans ⁶⁶	55	¹³¹ I ¹³¹ I		15 -147	57	8		11
Chapman ⁶⁵	48	¹³¹ I	140	4 - 14	36	12		
Soley and Miller ³¹⁰	33	¹³¹ I		0.5- 9.1	25		8	
Williams et al ³⁹⁰	80	¹³¹ I		8.5	76			4
Werner et al ³⁷⁸	34	¹³¹ I	75	2.9- 8.6	30			4
Haines and Keating ¹³³	55	¹³¹ I	250	2.6- 20	45	6	4	15
Feitelberg et al ¹¹⁷	290	¹³¹ I	80	1.7- 11	278		2	13

The physical units of Werner et al do not agree with the other authors as Geiger counters at the College of Physicians and Surgeons were standardized by ionization chamber measurements. Intercomparison of ¹³¹I standards by various laboratories in England, United States and Canada verified the accuracy of absolute activity measurements to the order of ± 2 per cent.³¹¹

[c] 'Effective half life'
(amount of iodine
in gland decreases
both by decay and
by excretion)

[2] Determine total urinary
excretion of radioiodine
for first 72 hrs

(d) Desirable to express doses
in terms of equivalent roent-
gens [successful dose in
approximately 15,000 to
30,000 e.r. (equivalent
roentgens)]

[1] Roentgen, as defined by
international agreement,
applies only to λ or
gamma radiation and
cannot be used for radi-
ation due to primary
beta particles

[2] Equivalent roentgen
or 'rep' ('roentgen
equivalent physical' of
the Plutonium Project)
so that amount of beta
radiation which, under
equilibrium conditions
releases in 1 Gm of air
(approximately 83 ergs)
or soft tissue (approx-
imately 93 ergs) as
much energy as one
roentgen of gamma rays

(c) Known average energy per
disintegration and half life
in days of radioiodine used

(2) Formula^{114, 139, 311, 393}

(a) Determination of thera-
peutic dose (in microcuries)

C =

(Microcuries desired per Gm.
of thyroid) $\times 100 \times$ (esti-
mated thyroid weight in Gm)
Per cent of ¹³¹I tracer col-
lected by thyroid

(b) Determination of equivalent
roentgens ($e.r. = D\beta + D\gamma$)

[1] $D\beta = \frac{88 E\beta T C}{\text{per microcurie de-}} \frac{e.r.}{\text{stroyed per Gm}}$
T—the half life of the
isotope in days

$E\beta$ —the average energy
per disintegrations
of the beta rays
in million electron
volts

C—the known empiric
initial concentra-
tion of microcuries
per Gm of esti-
mated thyroid tis-
sue

[2] $D\gamma = k\gamma C\gamma$ roentgens

(c) K_y is the number of roentgens at 1 cm distance in air due to complete disintegration of an unfiltered point source of one microcurie

(d) g is a geometric factor depending on the size and the shape of the tissue mass under consideration and on the absorption of gamma rays (g for thyroid is approximately $4 \pi R$)

(e) R = radius of one lobe of thyroid (estimated)

$$\begin{array}{l} {}^{130}\text{I} \left\{ \begin{array}{l} E\beta = 0.270 \text{ Mev} \\ T = 0.525 \text{ days} \\ K_y = 0.237 \end{array} \right. \quad {}^{131}\text{I} \left\{ \begin{array}{l} E\beta = 0.205 \text{ Mev} \\ T = 8.0 \text{ days} \\ K_y = 0.735 \end{array} \right.$$

(3) Maximum tolerance dose without serious after-effects is not yet determined

(4) Single doses of 250 microcuries of ${}^{131}\text{I}$ have been given without serious toxic effect

(5) Methods of increasing uptake of radioiodine

(a) Thyrotropic hormone in injection²⁰

(b) Removal of normal thyroid by

{1} Surgery

{2} Roentgen therapy

(c) Antithyroid drug administration and withdrawal a few days before giving radioiodine

(d) Temporary renal block of radioiodine excretion²²⁰

5 Clinical response^{20 125 147 143 231 280}

a Temporary exacerbation of thyrotoxicosis and increased basal metabolic rate due to greater release of thyroid hormone by irradiated tissues⁶⁹

(1) This is usually found when ${}^{130}\text{I}$ is chief source of radiation

(2) Prophylactic ingestion of ordinary iodine or anticipation of this response will effect the radioiodine by

(a) Increasing its secretion

(b) Diminishing its therapeutic action²⁴⁵

b Basal metabolic rate decreases in from 2 to 6 weeks

c Cholesterol (plasma) increases

d Transient hypothyroidism or myxedema

e Fibrosis of thyroid

J PARA-AMINOBENZOIC ACID^{1 121 270 287}

1 Indication—none, discarded now

2 Dosage

a Oral—1 gr q i d

b Parenteral—1 gr 6 times weekly

3 Results

a Weight—increased

b Pulse—decreased

c Cholesterol (plasma)—increased

d Basal metabolic rate—decreased

4 Toxic reactions¹²¹

a Bone marrow depressed

b Renal damage

c Liver may show fatty infiltration

J ESTROGENS^{73 116 170 200 208 219 275 321 341 347 348}

1 Indication—experimental

2 Dosage (any estrogenic preparation)

a Oral—1 to 4 mg daily

b Parenteral—210,000 to 3 410,000 Iu over 6 to 16 weeks

c Total amounts used and duration of therapy are variable

3 Results (diverse reports)

a Subjective complaints are improved

b No effect on

(1) Exophthalmos

(2) Gouty size

c Cholesterol (plasma) changes are irregular

d Basal metabolic rate may be lowered

J GENERAL

1 Diet

a Calories—3,000 daily if possible

b Protein

(1) 100 to 150 Gm at least daily^{1 4}

(2) Low intake aids iodine therapy

c Intravenous therapy may be necessary for

(1) Nausea

(2) Vomiting

J 2 Vitamin B complex in sufficient amounts

J 3 Calcium intake should be adequate although its clinical importance is questionable

4 Testosterone (see 107 VII A)¹⁰⁰

- a Indication—to reduce nitrogen loss
- b Dosage
 - (1) Oral—50 mg daily
 - (2) Intramuscular—25 mg daily or every other day during preoperative period
- 5 Sedation to relieve
 - Tension
 - b Restlessness
 - c Insomnia

L SURGICAL

1 Historical data

- Multiple stage operations (prior to 1912)¹¹⁵

(1) Pole ligation

- (a) Procedure — one or both superior and/or inferior thyroid arteries are tied in preparation for partial thyroidectomy

(b) Results

- [1] Temporary amelioration
- [2] No change
- [3] Exacerbation
- [4] Thyroid storm
- [5] Death

(2) Partial or hemithyroidectomy (prior to 1912)¹¹⁵

- (a) Procedure — one half of gland is removed

(b) Results

- [1] No apparent effect (rare)
- [2] Thyroid storm
- [3] Complications
 - [a] Tetany
 - [b] Vocal cord paralysis
- [4] Basal metabolic rate
 - [a] Decreases about 50 per cent (average)
 - [b] Returns to normal (with iodine)
- [5] Death

(3) Subtotal thyroidectomy or a second hemithyroidectomy (about 1912-1930)¹⁷⁸

- (a) Procedure — almost complete removal of both lobes
 - [1] Return to normal of
 - [a] Weight

[b] Pulse

[c] Basal metabolic rate

[2] Persistence of disease in some

[3] Postoperative myxedema

[a] Temporary

[b] Permanent

[4] Thyroid storm

[5] Complications

[a] Tetany

[b] Vocal cord paralysis

[6] Death

(4) Radical subtotal thyroidectomy (about 1930-1942)¹⁷⁸

(a) Procedure — radical resection of both lobes

(b) Results

[1] As above

[2] Persistent hyperthyroidism practically eliminated

(5) Thiouracil era

(a) Multiple stage operations discarded

(b) Postoperative reactions abolished by antithyroid drugs which prevent hypersecretion of unresected thyroid remnants

(c) Friability and vascularity produced by antithyroid drugs decreased by additional use of iodine

(6) Mortality¹¹⁵ PER CENT

(a) Prior to 1912 (average) 9

(b) Multiple stage operations 2 3

(c) Iodine and fewer surgical procedures (estimate) 1 3

(d) To date Less than 0 15

(7) Persistence of disease¹⁷⁸ PER CENT

(a) Before 1912 (partial thyroidectomy) 10-90

(b) 1912-1931 (subtotal thyroidectomy) 10

(c) 1930-1942 (radical subtotal thyroidectomy) Less than 1

(d) To date Less than 1

2 Subtotal thyroidectomy (See Figs 199 202)

a Intratracheal nitrous oxide oxygen and ether anesthesia

b Curved collar incision usually 2 cm above clavicles

c Division of fat and platysma

d Incision of deep cervical fascia

■ Free each sternocleidomastoid muscle

f Midline incision through deep fascia from thyroid cartilage to sternal notch

■ High transverse division of sternohyoid and sternothyroid muscles

h Partial division of omohyoid muscle

i Elevation of right lateral lobe with medial retraction

j Division of middle thyroid veins

k Complete lateral dissection and retraction of carotid sheath and its contents

l Identification and ligation in continuity of inferior thyroid artery

m Exposure of recurrent laryngeal nerve over full course in neck

n Exposure of inferior parathyroid

o Double ligation and division of superior thyroid artery and vein

p Identification of superior parathyroid (provisional)

q Subtotal excision of lateral lobe and total removal of isthmus and pyramidal lobe leaving small remnant

r Reconstruction of remnant to tracheal fascia

s Identical steps for subtotal excision of left lobe

t Reinspection of all anatomy and vessel pedicles

■ Suture of prethyroid muscles and deep cervical fascia

v Closure of platysma and skin with clips

w Wound is closed without drains

M MANAGEMENT OF COMPLICATIONS

✓ 1 Acute thyroid crisis or thyroid storm

a Crisis before or after surgery

(1) An urgent situation

(2) This should not occur after operation if patient is properly prepared with thiouracil and/or iodine (see Chart 60)

b Precipitating causes^{23r}

(1) Emotional strain

(2) Acute infection

(3) Gradual exacerbation of hyperthyroidism

(4) Unknown factors

(5) Subtotal or hemithyroidectomy

c Symptomatology

(1) Restlessness extreme

(2) Delirium

(3) Psychoses

(4) Hyperpyrexia

(5) Tachycardia marked

(6) Auricular fibrillation (see below)

(7) Anorexia

(8) Nausea

(9) Vomiting

(10) Diarrhea

(11) Jaundice

(a) Occasional case

(b) Mild

(12) Exhaustion eventually

(13) Coma

d Treatment

(1) Morphine— $\frac{1}{6}$ to $\frac{1}{4}$ gr hypodermically by the clock to control restlessness

(2) Fluids

(a) Dosage

[1] Intravenous—5 per cent glucose in saline 3 000 to 4 000 cc interrupted or continuously

[2] If diabetic, add insulin

(3) Lugol's solution—10 to 30 minims daily mixed with above intravenous fluids

(4) Oxygen—may be tried but often is not well tolerated

(5) Penicillin or sulfonamides for prophylactic purposes in adequate 24 hr doses

(6) Propylthiouracil administration orally as soon as it can be maintained in preoperative thyroid crisis

(7) Exophthalmos—protect conjunctivae by use of ointments (see below)

2 Acute congestive heart failure with thyroid crisis—see 30 XIII B

3 Chronic congestive heart failure with

out acute cardiovascular symptoms—
see 30 XIII C

✓ 4 Exophthalmos

a Complications

- (1) Acute conjunctivitis
- (2) Acute edema
- (3) Optic nerve edema rarely develops
- (4) Lid retraction
- (5) Eyeballs may "fall out"

b Treatment—see 33 XIV

■ Results—see 33 XIV D 1 d

5 Acute infections

■ Types—any kind possible

b Treatment—for specific infection

c Results—good in majority

6 Laryngeal and tracheal complications

109

a Causes (some may be present preoperatively)

(1) Edema and/or ecchymosis in tissues of

- (a) Neck
- (b) Larynx
- (c) Trachea

(2) Hemorrhage into the wound

(3) Compression of larynx and trachea from

- (a) Above (1) and (2)
- (b) Thyroiditis
- (c) New growths
- (d) Enlarged thyroid gland

(4) Paralysis of one or both recurrent laryngeal nerves

- (a) Edema
- (b) Surgical trauma
- (c) New growth

(5) Tracheal obstruction from (1) to (4)

(6) Wound infection secondary to

- (a) Tracheotomy
- (b) Opening of pharynx

(7) Respiratory failure from morphine in thiouracil prepared patients

(8) Tetany—see below

b Symptomatology

- (1) Hoarseness
- (2) Dysphonia
- (3) Dyspnea (especially from hemorrhage)
- (4) Stridor (also due to excessive bleeding)

(5) Cough

(6) Dysphagia

c Treatment

(1) Wound hemorrhage

(a) Urgent for symptoms develop quickly

(b) If an emergency

- [1] Wound opened
- [2] Clot evacuated
- [3] Local pressure until bleeding stops
- [4] Tracheotomy may be indicated

(c) Surgery may be necessary if bleeding

- [1] Cannot be stopped
- [2] Occurs into the thoracic region

(2) Of other causes

(a) Air may be kept free of tenacious secretions by

- [1] Expectorants
- [2] Steam inhalations
- [3] Oxygen administration

(b) Tracheotomy may be necessary for relief of obstruction, unless aided by evacuation of clot (see above)

- [1] For temporary help, an intratracheal tube is inserted through the mouth or the nose and past the obstruction in the larynx or trachea providing

[a] Time to arrange for tracheotomy

[b] Means for administration of oxygen or anesthetic

- [2] Tube should be placed below first tracheal ring

(c) Antibiotics may be used to prevent or control infection when tracheotomy is present

(3) Unilateral recurrent nerve paralysis (vocal cord paralysis)

(a) Symptomatology — hoarseness only

(b) Treatment

- [1] None
- [2] Patient must refrain from forcing voice

- (c) Prognosis
 [1] Patient should be re assured
 [2] A good speaking voice will be obtained within a few weeks or months in nearly all cases
- (4) Bilateral recurrent nerve paralysis
- (a) Types
 [1] Temporary
 [2] Permanent
- (b) Symptomatology
 [1] Temporary paralysis if the vocal cords do not approximate then aphonia only or if they do
 [a] Dyspnea
 [b] Labored respiration
 [c] Voice may be quite good
 [2] Permanent paralysis
 [a] Air hunger with overexertion
 [b] Roaring noises during sleep so much that others cannot sleep in the vicinity
 [c] Inspiratory crow
 [d] Good voice
- (c) Treatment of paralysis
 [1] Temporary—relieve obstruction until function returns (tracheotomy)
 [2] Permanent
 [a] Prevention of recurrent nerve injury — most important thing
 [b] Tracheotomy tube (Tucker valve tube which permits in halation through tube and exhalation through larynx) for relief of dyspnea patient has a good voice
 [c] Operative procedure — suture of nerve is unsuccessful
- (d) Prognosis
 [1] Temporary—good
 [2] Permanent — tragedy when this injury occurs
- ✓ 7 Acute parathyroid tetany
- a Symptomatology
 (1) Carpopedal spasm
 (2) Numbness and tingling of
 (a) Hands
 (b) Feet
 (c) Side of face
 (d) Lips
 (3) Laryngeal spasm
 (4) Marked depression
 (5) Anxiety
 (6) Generalized convulsions
 (7) Delirium
 (8) Respiratory distress
- b Signs
 (1) Chvostek's sign positive and indicative but not pathognomonic
 (2) Trousseau's sign positive
- c Treatment
 (1) For acute tetany and immediate results
 (a) Calcium chloride or gluconate
 [1] Dosage
 [a] Intravenous—10 to 20 cc of 10 to 20 per cent solution slowly
 [b] Repeat as necessary
 (b) Glucose—50 to 500 cc of 5 to 20 per cent solution intravenously
 (c) Parathyroid extract (parathyroid hormone)—100 to 300 units parenterally repeat in 12 hrs if necessary
 (2) For subsequent control (to be given at onset) any of the following may be used
 (a) Dihydrotachysterol (A T 10)
 [1] Initial — 1 cc tid orally
 [2] Maintenance — reduce later when blood calcium is normal
 (b) Vitamin D
 [1] Initial—50 000 to 100 000 units orally daily

- [2] Maintenance — reduce dosage later to patient's requirement
- (c) Calcium lactate—6 to 10 Gm daily dissolved in hot water or any palatable hot liquid
- (3) For chronic parathyroid deficiency—see 37 VII B
- 8 Paroxysmal auricular fibrillation or flutter—see 30 VIII D
- 9 Pulmonary complications
 - a Acute upper respiratory infections
 - (1) Variable severity
 - (2) Occurrence may precede other lung complications
 - b Bronchopneumonia
 - (1) Prophylactic measures
 - (2) Steam inhalations as necessary
 - (3) Antibiotic preparations
 - c Atelectasis
 - (1) Etiology—mucus plug is most common
 - (2) Treatment
 - (a) Frequent turning of patient may prevent this
 - (b) Bronchoscopy
 - d Injury to the pleural cupula¹⁴⁰
- 10 Postoperative embolus
 - a Pulmonary—practically unknown
 - b Arterial—exceedingly rare but has been observed several times in patients with auricular fibrillation with or without rheumatic heart disease
- 11 Injury to esophagus (rare)¹³⁴
- 12 Later developments
 - a Postoperative myxedema (see 25 XVI, Chart 61)
 - (1) Symptoms may be noticed within a month by patient although clinical signs may take longer to appear
 - (2) Following an operation for diffuse hyperplastic hypersecretory goiter, myxedema may not be permanent (1 out of 3)
 - (3) Withholding treatment for myxedema may favor return of thyroid function but may also encourage recurrence of hyperthyroidism
 - (4) Administration of desiccated thyroid one half to 2 gr daily (as needed) relieves signs and symptoms of myxedema
 - (5) When tetany is also present, administration of thyroid for myxedema will help to control this
 - b Postoperative low basal metabolic rate without myxedema¹⁷⁸
 - (1) Occasionally associated with amenorrhea, origin may be in the
 - (a) Pituitary
 - (b) Hypothalamus
 - (2) Low basal metabolic rate may have existed prior to onset of toxic goiter, but there is no way to prove this
 - (3) Desiccated thyroid does not help much
 - c Postoperative hypercholesterolemia may¹⁷⁸
 - (1) Indicate thyroid deficiency usually
 - (2) Be transient
 - (3) Have existed before onset of hyperthyroidism (see Chart 62)
 - d Weight gain in excess
 - (1) Unusual
 - (2) Development in formerly obese individuals
 - (3) Greater caloric intake may be explanation
 - (4) Change in habits of eating after thyroidectomy
 - (5) Prescribed rest may be a factor
 - e Sensitivity to cold without signs of myxedema possibly in contrast with former heat intolerance¹⁷⁸
 - f Falling of hair¹⁷³
 - (1) Occurs often and does not mean myxedema
 - (2) May be due to relatively short period of thyroid deficiency
 - g Exophthalmos, postoperative persistence, development of, and/or progression (see 33 XIV)
 - h Muscular cramps¹⁷⁸
 - (1) Common
 - (2) Unexplained and of no importance
 - (3) Not associated with hypocalcemia
 - (4) Tetany however, should be excluded

- 1 Joint stiffness and arthritis^{17a}
 - (1) Hyperthyroidism often hinders up the arthritic patient
 - (2) Relief of hyperthyroidism may be followed by a return of joint symptoms

TABLE 25 DURATION OF HYPERTHYROIDISM BEFORE SURGICAL TREATMENT
(1016 cases treated before 1927)¹⁸³

YEARS	NO OF CASES	YEARS	NO OF CASES
1/4	124	4	43
1/2	189	5	48
1	252	7	21
2	118	10	38
3	60	Not stated	123

✓ N POSTOPERATIVE PROGRAM

- 1 Activity should be limited during the first few months with scheduled rest periods
- 2 Wholesome diet
- ✓ 3 Alcoholic beverages and tobacco (harm of latter has not been demonstrated) should be avoided in excess
- 4 Postoperative use of
 - a Iodine
 - (1) Little value
 - (2) Persistent or recurrent hyperthyroidism may be masked
 - (3) Myxedema may be produced
 - ✓ b Desiccated thyroid (U S P)
 - (1) As a routine procedure may have merit⁹⁵
 - (2) Dosage— $\frac{1}{2}$ to 1 gr daily
- 5 Periodic checkup—basal metabolic rate desirable especially 3 months after operation
- 6 Digitalis—continued use may be necessary to control the heart rate with persistent auricular fibrillation
- 7 Pregnancy
 - Inadvisable for at least a year after cure
 - b Safe if no recurrence of hyperthyroidism

(b) Return when medication is discontinued

b Thiouracil

- (1) Euthyroid state obtainable in most instances
- (2) Duration of remission varies
- (3) Continual administration necessary to ensure remission
- (4) Relapse rate high^{95, 11, 286}
- c Radioactive iodine—final evaluation has yet to be made
- d Roentgen irradiation of thyroid
 - (1) Mild cases may have a permanent cure
 - (2) Severe hyperthyroid patients
 - (a) Temporary relief
 - (b) Refractory
 - (3) Procedure is not used at present except for
 - (a) Recurrence of the disease
 - (b) Persistent cases
- At present thiouracil and iodine are indicated chiefly in preparation of patients for surgery

XVII PROGNOSIS

A UNTREATED

- 1 Disease may rarely be self limited
- 2 Fatal acute thyroid crisis may occur within a relatively short time^{22a}
- 3 Hyperthyroidism may persist for years with exacerbations but complete remissions of long duration are uncommon

B TREATED

- 1 Medical
 - a Iodine
 - (1) Relief of active symptoms in
 - (a) Mild cases
 - (b) Severe cases partially
 - (2) Disease may
 - (a) Become more intense

2 Surgical (see Figs 203 and 204)

a Factors affecting therapy

- (1) Pre antithyroid drug era the outcome was dependent upon
 - (a) Patient's age
 - (b) Duration of disease
 - (c) Severity of disorder
 - (d) Preoperative response to iodine
 - (e) Skill and experience of surgeon
 - (f) Anesthesia
- (2) Thiouracil era
 - (a) Surgical mortality practically eliminated so that most of the above factors are less important

- (b) Three deaths in 1,850 operated cases from 1942 to 1950
- b Life expectancy following surgical treatment
- (1) Exact morbidity not known
 - (2) The life span of thyrocardiacs is less than that of uncomplicated hyperthyroidism (see 30 \IV)
 - (3) Persistence of auricular fibrillation after cure of hyperthyroidism apparently does not shorten life
 - (4) Recurrence or persistence of hyperthyroidism tends to increase morbidity and complications, if further operations on the thyroid are undertaken
- c Results of subtotal thyroidectomy for primary hyperthyroidism—see Tables 26 and 27

TABLE 26 · PRETHIOURACIL ERA

Statistics from the Follow up of 1,016 Cases Operated upon Prior to 1927¹⁸

	CASES
Tetany	
Permanent	7
Transient	4
Cord paralysis	
Unilateral	2
Bilateral	1
Permanent auricular fibrillation following operation	33
Myxedema	
Permanent	49
Temporary (requiring temporary treatment)	22
Operative mortality	
All	16 (1.5%)
Cases with auricular fibrillation	5 (8.4%)

TABLE 27 · THIOURACIL ERA

Complications of Subtotal Thyroidectomy (1 000 Cases)^{18a}

	PER CENT
Tetany	
Permanent	1.5
Transient	1.2
Vocal cord paralysis	1.0
Permanent myxedema	4.2
Mortality	0.2

d Interval results following therapy—see Tables 28 and 29

TABLE 28 · TEN TO 20 YEAR RESULTS OF SUBTOTAL THYROIDECTOMY*
Prethiouracil Era¹⁸

No of CASES	RESULTS	DESCRIPTION
386	Excellent	No complaints patient in good health
139	Good	Persistent auricular fibrillation persistent hyperthyroidism controlled or myxedema regulated with thyroid all in satisfactory condition
38	Fair	Ambulatory condition fair but may not be entirely due to thyroid condition if present
26	Poor	Usually incapacitated poor health outcome is not always the result of thyroid disease uncontrolled hyperthyroidism included

* General condition of 589 cases of the original 1 016 cases of primary hyperthyroidism contacted for 10 to 20 years after operation. Similar results have been reported by others.³⁶⁵

TABLE 29 · RESULTS OF SUBTOTAL THYROIDECTOMY (462 CASES)
Thiouracil Era⁷⁷

	PER CENT
Two year follow up	95
Recurrence	2.2
Reoperation	0.8
Controlled with Lugol's solution	1.0
Roentgen therapy	0.2
Persistence	0

XVIII CAUSES OF DEATH¹⁸

A SUMMARY

- 1 Thyroid crisis (see Fig 205)
- 2 Acute cardiac decompensation
- 3 Hepatic failure
- 4 Bronchopneumonia
- 5 Alarm reaction possibly—thymus and lymph glands are unable to release immune globulins to aid in state of assistance
- 6 Preoperative
 - a Before surgery completed (pre thiouracil era)—5 out of 1,016 cases (prior to 1927)

b This can happen now if iodine is not administered simultaneously with antithyroid drugs in severe cases while awaiting for the latter to take effect

TABLE 30 CAUSES OF DEATH IN HYPER THYROID PATIENTS AFTER SURVIVING SUBTOTAL THYROIDECTOMY¹⁹² (10 to 20 Year Follow up of 589 Cases)

	No of Cases
Cardiovascular disease	14
Cancer	5
Pneumonia	3
Old age	2
Diabetic coma	1
Tetany	1
Childbirth	1
Myasthenia gravis	1
Suicide	1
Postoperative deaths from hernia peritonitis etc	4

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FIG 184 HYPERSECRETORY HYPERPLASTIC GOITER
AGE

FIG 183 HYPERSECRETORY HYPERPLASTIC GOITER Diffusely enlarged gland and hyperthyroidism in a child age 3 (Cattell R B Thyroid disorders in childhood New England J Med. 209 867 875)



- 5 Height 46 in Height age 7
- 6 Picture above Eyes became prominent at the age of 1½ years Goiter noted as well as palpitation sweating and nervousness No weight loss Weight 40 lbs Height age 6 6 years Pulse 130 BMR plus 60% After iodine for 14 days weight 42 lbs pulse 80 and BMR plus 4% Subtotal thyroidectomy Pathologic diagnosis hyperplasia
- 7 Weight 50 lbs Height 48¾ in Height age 8 Pulse 96 BMR minus 20% Eyes unchanged (Cattell R B Thyroid disorders in childhood New England J Med 209 867 875)

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FIG 188 VITILIGO Age 28 After child birth extensive vitiligo and hyperthyroidism developed Duration 1 year Weight loss of 24 lbs Weight 102 lbs Pulse 110 BMR plus 84% Four years later weight 128 lbs pulse 80 BMR 0% vitiligo increased



FIG 189 HYPERSECRETORY DIFFUSE HYPERPLASTIC GOITER Age 53 female Undermining of nails in hyperthyroidism (top) and improvement after 69 days of thouracil treatment (bottom)



FIG 190 UNILATERAL EXOPHTHALMOS AND OPHTHALMOPLÉGIA Age 44 Patient unable to raise right eye to look upward Exophthalmos of the affected eye and possibly some of the other although it appeared to be normal Prominence of eye was noted several months before symptoms of hyperthyroidism Before operation weight 117 lbs pulse 96 BMR plus 69% At the time of photograph which was taken 3 months after sub total thyroidectomy weight 140 lbs plus 72 BMR plus 9%



FIG 185 HYPERSECRETORY DIFFUSE HYPERPLASTIC GOITER (Left)
 Age 24 Marked exophthalmos and large hyperplastic gland with
 severe hyperthyroidism Pulse 128 BMR plus 69% Hemithyroid
 ectomy performed (Right) After second stage operation



FIG 186 HYPERSECRETORY DIFFUSE HYPERPLASTIC GOITER Moderate hyperthyroidism and enlarged hyperplastic gland without exophthalmos in a young man



FIG 187 HYPERSECRETORY DIFFUSE HYPERPLASTIC GOITER Moderate hyperthyroidism in an elderly man Stare, probably slight exophthalmos no visible goiter Small hyperplastic and pebbly gland

FIG 194 GRAVES'S DISEASE
SUPERIMPOSED ON NODULAR
GOITER Age 51 Goiter noted 5
years and 3 months before entry
Weight 135 lbs Pulse 132 BMR
plus 60% Ten days iodination
Weight 141 lbs Pulse 92 BMR
plus 24% Pathologic report mul-
tiple colloid adenomatous goiter
with hyperplasia BMR before
second hemithyroidectomy 2
months later plus 64% Weight
136 lbs Pulse 130 BMR plus
21% Ten days later with iodine
and rest Weight 137 lbs Pulse
104 BMR plus 27% Apparently
no iodine taken between opera-
tions The effect of iodine and rest
was unmistakable the gland was
adenomatous



Various Cardiothoracic Ratios in Toxic and Nontoxic Goiter

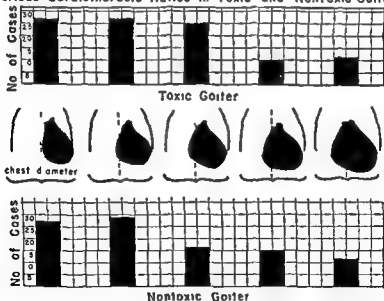


CHART 45 COMPARISON OF INCIDENCE OF VARIOUS CARDIOTHORACIC RATIOS IN 100 CASES OF TOXIC GOITER AND 100 CASES OF NONTOXIC GOITER The similarity is striking The incidence of enlarged hearts in non toxic goiter probably is due to a greater number of cases with cardio vascular disease which were referred on suspicion that goiter might be the cause of hypertension etc This illustrates the difficulty in determining the actual role played by hyperthyroidism on the heart when the latter is found to be enlarged in toxic goiter (Hurthall L M and Menard O J Changes observed in the heart shadow in toxic goiter before and after treatment Ann Int Med. 11 1634-1643)



FIG 191 CORNEAL ULCER IN HYPERSECRETORY DIFFUSE HYPERPLASTIC GOITER Age 28 Weight 134 lbs Pulse 96 BMR plus 32% One year after subtotal thyroidectomy weight was 152 lbs and BMR minus 5% Conjunctivitis of left eye developed postoperatively and with corneal ulcer Exophthalmos measured 30 mm bilaterally The outer wall of orbit was resected Prominence of eye reduced 7 mm No further contact with patient



FIG 192 UNILATERAL PARALYSIS OF SUPERIOR RECTUS MUSCLE Mild hyperthyroidism with slight exophthalmos and paralysis of superior rectus muscle on right Note position of right eye when looking straight ahead with left eye Unchanged by subtotal thyroidectomy



FIG 193 HYPERSECRETORY DIFFUSE HYPERPLASTIC GOITER (Left) Exophthalmos with tearing injection of scleras with edema of lids (Right) Improvement after operation

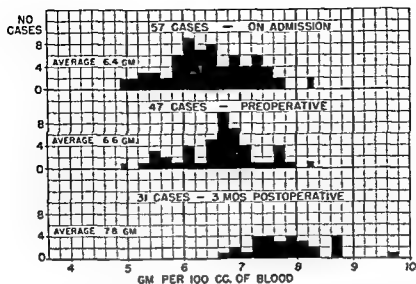


CHART 47 HYPERTHYROIDISM Total serum protein in hyperthyroidism before and after iodine administration and after subtotal thyroidectomy. The shift to the right is caused entirely by the serum albumin fraction. Initial average 3.4 Gm/100 cc. Final average 4.8 Gm/100 cc. (Bartels E. C. Adrenal gland in hyperthyroidism: cortical functions. West J Surg 48: 50-53)



FIG 196 HYPERSECRETORY DIFFUSE HYPERPLASTIC GOITER (Left) Heart shadow in a young woman age 31 with exophthalmic goiter auricular fibrillation and slight congestive heart failure. Weight 108 lbs. Pulse 98 BP 160/90 BMR plus 101%. Note prominence of pulmonary arc as well as region of left auricle. (Right) Heart shadow 12 months later. Normal rhythm present. Weight 120 lbs. Pulse 84 BP 140/90 BMR plus 11%. Still slightly toxic on Lugol's solution. The outline of each film is superimposed upon the other. Note marked reduction along left side with diaphragm at same level. The prominence of the pulmonary arc persists. (Menard O. J. and Hurxthal L. M. Changes observed on the heart shadow in toxic goiter before and after treatment. Ann Int Med. 6: 1634-1643)

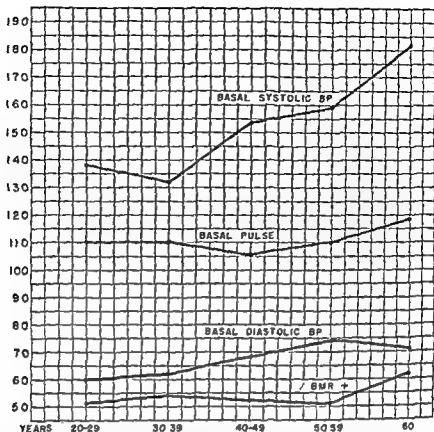


CHART 46 BLOOD PRESSURE IN HYPERTHYROIDISM (See Chart 52 for effect of return of normal thyroid function) Basal BP pulse and BMR plotted according to age groups in cases of hyperthyroidism requiring two-stage operations (severer than average) Note that the average BMR was approximately the same for all age groups while the basal systolic BP, as well as diastolic pressure rose with age (Hurvital L M Blood pressure before and after operation in hyperthyroidism Arch Int Med 47 167 181)



FIG 195 MUSCULAR ATROPHY IN SEVERE HYPERTHYROIDISM (Top) Before treatment (Bottom) After propylthiouracil (Bartels E C and Pizer E Muscular atrophy in hyperthyroidism Report of a case Lahey Clin Bull 4 52 58)

B Hypersecretory Diffuse Hyperplastic Gout

- 1 The hypothetical starting point in this diagram is the hypothalamus
- 2 An excess of TSH is secreted which
 - a Produces changes in the eye and increase in intraorbital fat which may lead to exophthalmos possibly in conjunction with sympathetic system (?)
 - b Causes excessive stimulation of the thyroid cells and hyperplasia
 - c May be present in the urine in inactive form due to effect of thyroid cells
- 3 An excess of TH hormone is produced which
 - a Increases the
 - 1 Urinary iodine excretion
 - 2 Blood iodine (both fractions)
 - 3 BMR
 - b Inhibits the thyroid cells but not sufficiently
 - c May supply additional iodine to the thyroid
- 4 When the disease continues unabated without an adequate iodine intake the total amount of circulating iodine (free or protein bound) decreases because of its
 - a Quick utilization
 - b Excessive urinary excretion
- 5 At this point there is evidence of an enzyme which facilitates the breakdown of organic iodides which makes them readily available for the thyroid cells but also renders them more liable to loss through the kidneys

CHART 49 DIAGRAMS DEPICTING EFFECT OF IODINE AND THIOURACIL IN HYPERSECRETORY DIFFUSE HYPERPLASTIC GOITER.

A Iodine Therapy

- 1 Excess iodine is shown entering the blood stream with a great increase in total blood iodine (mostly inorganic)
- 2 Large amounts are available for thyroid cells which are shown here by four involuted follicles representing hypertrophy as well as previous hyperplasia
- 3 A great excess of iodine is found in the urine
- 4 Since the total output of the whole over active gland would seem to be proportionate to the number of follicles as well as the degree of overactivity it is obvious in this diagram that since the BMR is depicted as normal one of the following phenomena could have taken place
 - a All follicles were overactive and iodine reduced the BMR to normal the thyroid cells (before iodine) may have been functioning to only a half or a third of their ability
 - b Only a part of the follicles were hyperplastic and possibly secreting to their fullest capacity all other follicles being inactive
 - c If the number of follicles was increased but only a part were hyperplastic and

secreting to their fullest extent the others were involuted

- d The reduction of thyroid hormone output by iodine administration in only those follicles which were hyperplastic (the number of which represented only a portion of those present) was sufficient to reduce the metabolism to normal before hyperthyroidism developed (see pp 303, 306 and Fig 116 p 341)

B Thiouracil

- 1 Thiouracil preparations block TH production as indicated by short curved heavy black line to right of thyroid cells which are shown as being hyperplastic
 - 2 TSH continues unabated exophthalmos persists
 - 3 The inhibiting effect of TH on TSH is reduced
 - 4 An increase in exophthalmos would be expected but this is not evident by clinical observation except in rare instances
 - 5 Iodine is absorbed by thyroid cells causing a decrease in vascularity and various degrees of involution but apparently is not synthesized into thyroid hormone or its precursors (D and T fractions)
 - 6 The stimulating effect of TH directly on the eyes is also lost which may account for nonprogression of exophthalmos (see above)
- On the other hand TSH administration to animals produces exophthalmos regardless of the removal of the pituitary the thyroid or the gonads. It is obvious that the theory does not fit the facts

CHART 50 DIAGRAMMATIC PRESENTATION OF VARIOUS RELATIONSHIPS AND PHENOMENA IN EXOPHTHALMIC SYNDROME AND PRIMARY MYXEDEMA

A Exophthalmos without Hyperthyroidism

- 1 Excess TSH and its nonutilization or rejection by the thyroid cells is demonstrated
- 2 Urinary TSH is found in the active form
- 3 Exophthalmos is shown
- 4 Thyroid cells are cuboidal
- 5 Blood and urinary iodine are normal
- 6 BMR is normal

B Primary Myxedema

- 1 Excess TSH is present in the blood
- 2 Urinary TSH is found in increased amounts in the active form
- 3 Blood iodine (total and organic) is reduced
- 4 It is difficult to correlate the absence of exophthalmos in myxedematous animals with an excess of TSH
- 5 The above diagrams may also represent a period of myxedema following subtotal thyroidectomy or a stage in the development of endemic goiter
- 6 If spontaneous myxedema is due in some instances to selective deficiency of pituitary TSH excess TSH would not be found in the urine

CHART 48

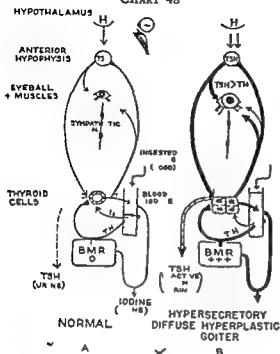
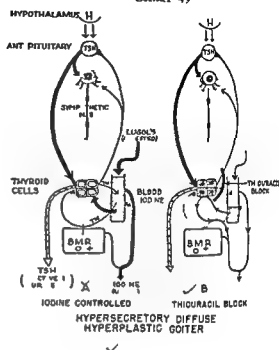


CHART 49



EXPLANATION OF SYMBOLS FOR CHARTS 48-50

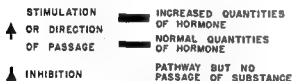


CHART 48 DIAGRAMMATIC PRESENTATION OF VARIOUS RELATIONSHIPS AND PHENOMENA WITH NORMAL AND HYPERSECRETORY DIFFUSE HYPERPLASTIC GOITER

A Normal Thyroid Gland

- The original stimulus is pictured as coming from H (hypothalamus) which arouses the pituitary thyrotropic hormone (TSH) to stimulate the thyroid cells represented here by normal resting cuboidal epithelium of one follicle
- TSH is thus utilized and none is excreted in the urine in the active form
- Thyroid hormone (TH)
 - Inhibits and regulates TSH secretion
 - Effects body cells directly
 - Maintains normal metabolism
 - Inhibits thyroid cells
- Iodine is
 - Released with utilization of TH by the tissues
 - Sent into the blood stream
 - Broken into smaller fragments by liver excreted in bile reabsorbed by intestine re enters blood stream
 - Reabsorbed by the thyroid cells
 - Excreted in the urine

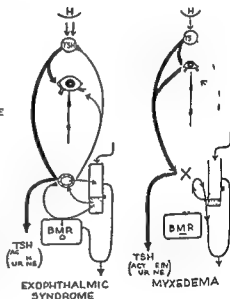


CHART 50

- Ingested iodine contained in diet enters the blood stream and follows same process as liberated iodine (above)
- The normal level of blood iodine and hormone is marked by a block square attached to the container which represents the volume of circulation blood
- Cervical sympathetic system and eyes are so designated
- The whole relationship is normal and in balance

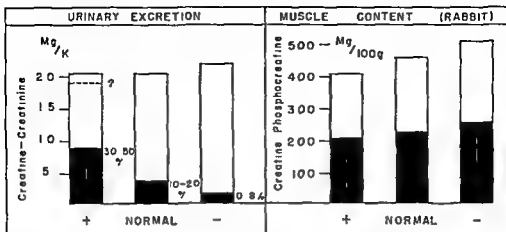


CHART 51 EFFECT OF HYPERTHYROIDISM AND HYPOTHYROIDISM ON URINARY AND MUSCLE CREATINE (Wilkins L. Conferences on Metabolic Aspects of Convalescence 10th Meeting June 15 16 New York Macy p 100)

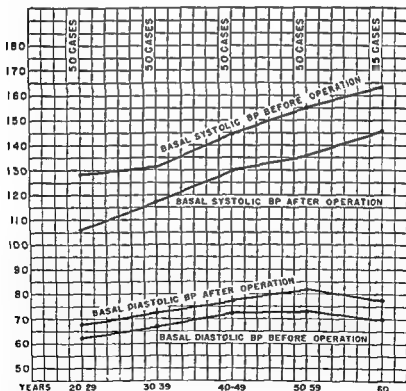


CHART 52 BLOOD PRESSURE IN HYPERTHYROIDISM Effect of subtotal thyroidectomy on average basal BP values 6 to 12 months after operation Plotted by age groups Note rise with age and drop in systolic pressures and rise in diastolic pressures All readings taken at time of metabolism test (Hurxthal L M Blood pressure before and after operation in hyperthyroidism Arch Int Med 47 167 181)

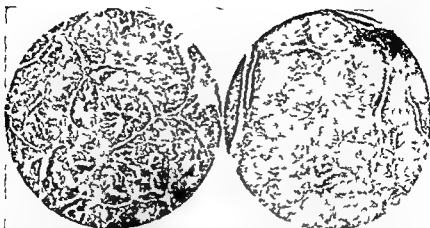


FIG 19. HYPERSECRETORY DIFFUSE HYPERPLASTIC GOITER (Left) Low power The microscopic appearance of thyroid gland in severe Graves's disease of long standing. No iodine had been given. The iodine content was 0.3 mg/Gm of dried gland. No colloid is visible. This specimen was obtained by hemithyroidectomy. (Right) Low power. A 6 weeks interval elapsed after the first operation during which time no iodine had been given. The iodine content of this specimen was unchanged. These pictures are representative of a group of patients used as controls in studying the effect of iodine on the hyperplastic gland in Graves's disease (Cattell R B. The pathology of exophthalmic goitre. Boston M & S J 192 989 996)

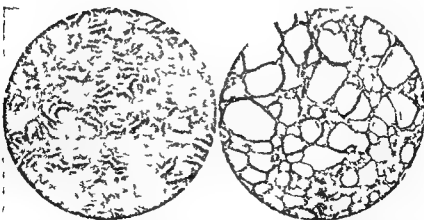


FIG 198. HYPERSECRETORY DIFFUSE HYPERPLASTIC GOITER (Left) Low power. Severe hyperthyroidism of 3 years duration with typical hyperplasia. Little colloid can be seen. The iodine content was 0.32 mg/Gm dried gland. (Right) Low power. Six weeks following the administration of Lugol's solution. Complete involution is present with the appearance of a normal or colloid gland. Marked clinical improvement. The iodine content was 5.4 mg/Gm dried gland. Involution is similar but less marked than if thouracil had been given along with iodine (Cattell R B. The pathology of exophthalmic goitre. Boston M & S J 192 989 996)

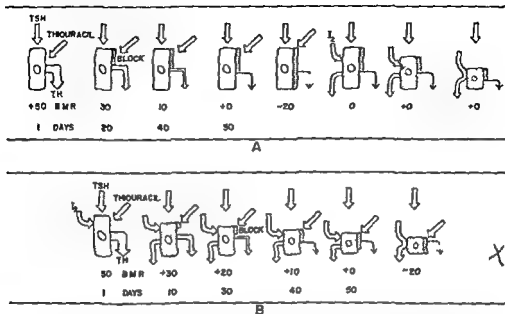


CHART 54 MECHANISM OF THIOURACIL AND IODINE ON THYROID CELLS Schematic representation of relationship between thyroid hormone (TH) and thyrotrophic hormone (TSH). Effect of thiouracil preparations and iodine in hypersecretory diffuse hyperplastic goiter. (A) Upper set of figures shows increasing block produced by thiouracil on hyperplastic thyroid cell. Thiouracil is continued until cell is putting out so little thyroid hormone (TH) that BMR is down to minus 20%. It is then stopped and iodine is given which involutes cell and BMR gradually rises as thyroid hormone is resynthesized and secreted. Dotted cells depict iodine storage. (B) Lower set of figures shows mechanism when iodine and thiouracil are given together. First iodine involutes the cell causing decreased output of thyroid hormone (TH). Thiouracil is then less effective when cells are involuted. Urinary iodine excretion not depicted here except when thyroid cell is saturated with iodine. In all cases when therapeutic doses of iodine are given there is an excess of urinary iodine.

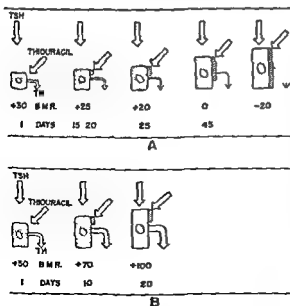


CHART 55 MECHANISM OF THIOURACIL AND IODINE ON THYROID CELLS (A) Schematic representation of effect of thiouracil on iodinated hypersecretory hyperplastic goiter. The partially involuted thyroid cell (cuboidal) is shown gradually becoming hyperplastic (columnar) without further iodine administration. Eventually marked hyperplasia with low BMR. Time required for effect of thiouracil is longer than a non iodinated gland (45 days for BMR plus 30%). Urinary iodine secretion is not depicted here. (B) Thiouracil administered to very severe case of Graves' disease in or approaching thyroid crisis. Slower action of thiouracil prevents immediate reduction in thyroid hormone output so that death might ensue before thiouracil is effective. Iodine should be given at once.

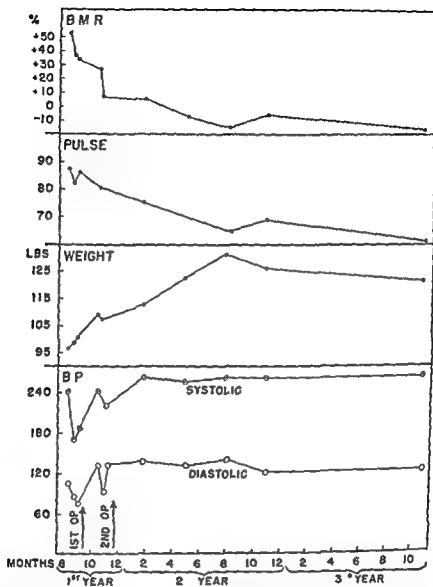


CHART 53 HYPERTENSION AND HYPERTHYROIDISM Observations over a period of 2½ years. Note drop in BP in hospital with bed rest. Subtotal thyroidectomy in 2 stages followed by normal BMR, and pulse rate with a weight gain of 40 lbs. The average diastolic and systolic BPs were higher after operation when hyperthyroidism was relieved completely. (Hurxthal L. M. The heart in hyperthyroidism. *New England J Med* 208: 538-541)

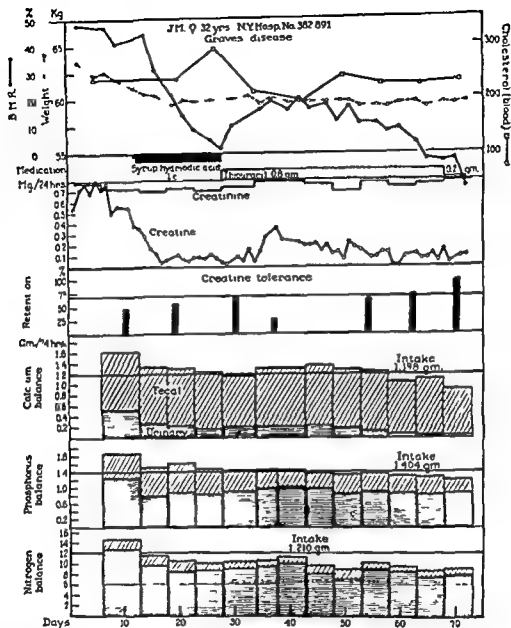


CHART 58 TREATMENT OF HYPERSECRETORY DIFFUSE HYPERPLASTIC GOITER Use of iodine followed by thiouracil showing relapse while on thiouracil and demonstrating importance of using iodine for quick response and thiouracil for later response in severe hyperthyroidism especially bordering on or in thyroid crisis Note also creatine excretion (Barr D P and Shorr ■ Observations on treatment of Graves disease with thiouracil Ann Int Med 23 754-778)

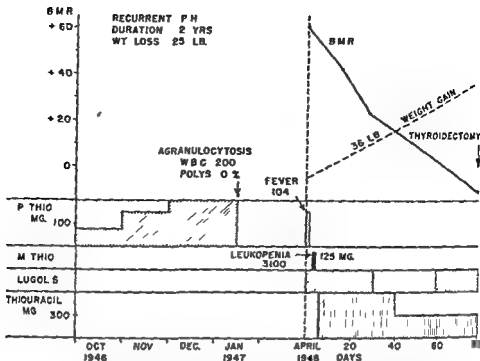


CHART 56 AGRANULOCYTOSIS FOLLOWED BY FEVER FROM PROPYLTHIOURACIL SENSITIZATION. Propylthiouracil caused agranulocytosis. On readministration a fever of 104 F resulted. Leukopenia also followed use of methylthiouracil. The patient was then tolerated until patient became euthyroid. Note immediate effect of Lugol's solution on a severe hypersecretory, diffuse hyperplastic goiter when given with propylthiouracil. This illustrates its advantage in cases threatened with thyroid crisis (Bartels E C and Ingham G K. Methylthiouracil an antithyroid drug. Lahey Clin Bull 6 174 180)

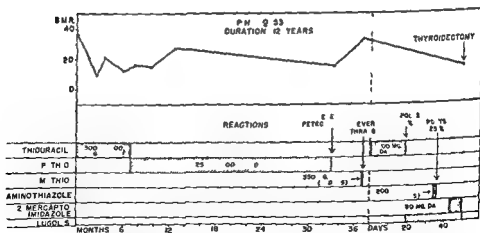


CHART 57 BLOOD CHANGES FROM ANTITHYROID DRUGS. Chart shows reactions to 4 antithyroid drugs and final control with mercaptoimidazole and Lugol's solution. P Thio = Propylthiouracil. M Thio = Methylthiouracil. (Bartels E C and Ingham G K. Methylthiouracil an antithyroid drug. Lahey Clin Bull 6 174 180)

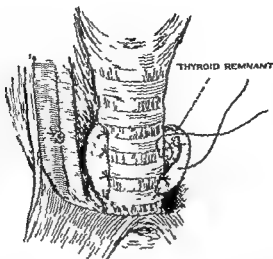


FIG 202 TECHNIC OF SUBTOTAL THYROIDECTOMY This illustration as seen in other technical descriptions of subtotal thyroidectomy shows the remnant of the thyroid which has been sutured against the trachea with 0 catgut stitches between the fascia covering the trachea and the edge of the thyroid. The cut surface of the thyroid with all of its tied vessels is sutured against the trachea to control oozing (Lahay F H. Technique of subtotal thyroidectomy. S Clin North America 29 641 658)

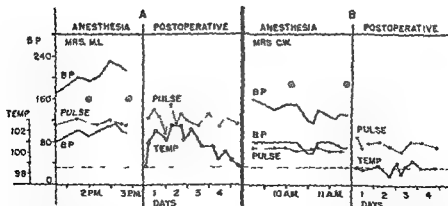


CHART 59 OPERATIVE BEHAVIOR IN HYPERTHYROIDISM A comparison of the anesthetic operative and postoperative course in a patient prepared with (A) Lugol's solution and (B) thiouracil (Bartels). C Thiouracil its use in the preoperative preparation of patients with severe hyperthyroidism. S Clin North America 25 645 650)

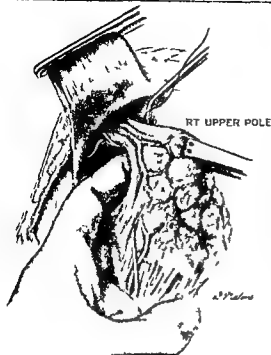
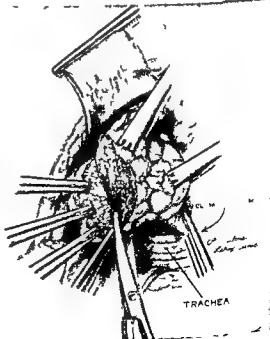
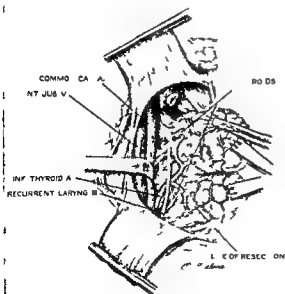


FIG 199 TECHNIC OF SUBTOTAL THYROIDECTOMY Method of separating the upper pole of the thyroid from its attachment to the larynx. The vessels can be completely freed and a ligature passed around them so that it does not include any of the apex of the upper thyroid pole. Note the finger tip placed beneath the upper pole to lift it away from the larynx. This maneuver ensures safe ligation of the superior thyroid artery and vein and even more important permits mobilization of the upper pole of the thyroid away from the larynx. The parathyroid which rests against the

larynx and behind this lobe can be exposed and preserved (Figs 199-201 from Lahey F. H. *Technic of subtotal thyroidectomy* S. Clin. North America 29: 641-658).

FIG 200 (Bottom left) TECHNIC OF SUBTOTAL THYROIDECTOMY The veins between the thyroid gland and the internal jugular vein are completely severed. The gland is lifted out of its bed and the region between the trachea and the common carotid is freed so that the inferior thyroid artery and the recurrent laryngeal nerve are exposed. In this illustration a step is shown which is not done until the lower pole has been mobilized but for the purposes of demonstrating the most common position of the upper parathyroid the superior thyroid pole is demonstrated as severed. The recurrent laryngeal nerve runs over the inferior thyroid artery. Note the relationship of the upper parathyroid and the recurrent laryngeal nerve as it enters the larynx in a position behind the latter where it rests before the superior thyroid artery and vein are severed. The upper pole is mobilized away from the larynx and inward to expose the parathyroid.

FIG 201 (Bottom, right) TECHNIC OF SUBTOTAL THYROIDECTOMY In the outer portion of the illustration the segment of thyroid into which the hemostats are plunged represents the portion of remaining gland. The isthmus is shown as clamped and has been completely separated from the trachea. The section of thyroid previously adherent to the trachea is cut by scissors until the entire lobe on that side is freed. With this portion of the operation completed the entire right lobe of the thyroid (except for the remnant together with the entire isthmus) is removed.



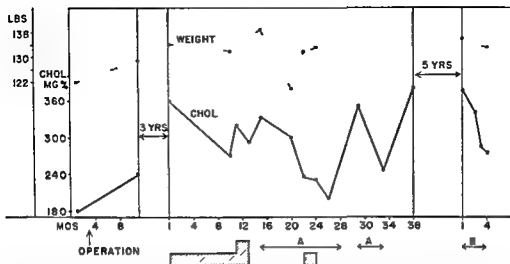


CHART 62 HYPERTHYROIDISM WITH NORMAL PLASMA CHOLESTEROL. Weight 122 lbs Pulse 100 Plasma cholesterol 186 mg % BMR plus 52% BMR after operation was always between minus 6% and minus 11% Plasma cholesterol values as shown No clinical evidence of myxedema Note that weight and plasma cholesterol increased or decreased together except on one occasion

Diagonal lined area = Desiccated thyroid 1 gr daily and a normal diet

Dotted square = Cholesterol (1 Gm a day) dissolved in olive oil

A = Low cholesterol diet (vegetable butter allowed no egg yolk meat fat cream or butter)

B = Egg yolk eliminated

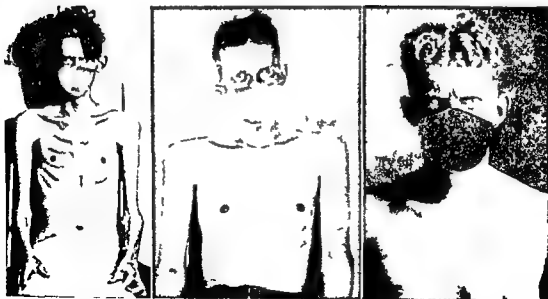


FIG 203 HYPERSECRETORY DIFFUSE HYPERPLASTIC GOITER (See also Fig 204) Severe hyperthyroidism and thyroid crisis (Left) Before operation (Center) After hemithyroidectomy (Right) Three months after completion of operation Weight gain from 90 to 150 lbs Note absence of chest hair Heart measurements were increased after treatment

THYROID DEATHS (2 cases)

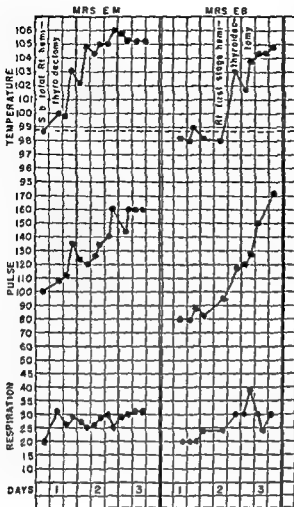
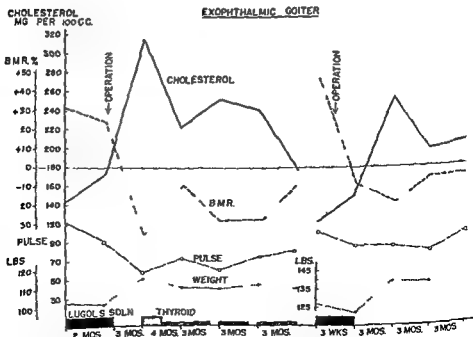


CHART 60 THYROID STORM
Typical postoperative temperature pulse and respiration chart in 2 patients dying in thyroid storm. These are not seen in patients properly prepared with antithyroid drugs

CHART 61 (Bottom) TEMPORARY AND PERMANENT POST OPERATIVE MYXEDEMA. Effect of iodine subtotal thyroidectomy and desiccated thyroid on plasma cholesterol BMR weight and pulse in (1) hypersecretory diffuse hyperplastic goiter subtotal thyroidectomy followed by myxedema requiring desiccated thyroid and (2) hypersecretory diffuse hyperplastic goiter with subclinical thyroid deficiency after subtotal thyroidectomy. No iodine or desiccated thyroid given after operation. The abnormal findings corrected themselves spontaneously. Solid block represents Lugol's solution. Shaded block equals 2 gr of desiccated thyroid (Hurxthal L. M. Blood cholesterol and thyroid disease III Myxedema and hypercholesteremia Arch Int Med 53 :62 1931)



CLINICAL VARIATIONS OF HYPERTHYROIDISM

Persistent	Associated with diabetes
Recurrent	Associated with pregnancy
Apathetic	Exophthalmic syndrome
Thyrocardiac patient	Factitious

SECTION 27

PERSISTENT HYPERTHYROIDISM

I DEFINITION

- A SUMMARY**—A persistence of hyperthyroid symptoms, although less severe, after medical treatment or surgical removal of seemingly adequate amounts of thyroid tissue
- NOTE** All findings are essentially the same as for hypersecretory hyperfunctioning goiter, except as indicated below

II PHYSICAL STATUS

- A THYROID REMNANTS**—Small to moderate size which are palpable within 3 months or more after operation located in region of isthmus if not previously removed hyperplastic and soft at first then becoming firmer as disease progresses
- B OTHER FINDINGS**—As before operation but less pronounced

III DIAGNOSIS

A SUMMARY

- 1 Borderline cases often present difficult diagnostic problems
- 2 It is important to ascertain if possible whether hyperthyroidism actually existed when the first operation was performed
- 3 If patient is on iodine or an antithyroid drug typical symptoms should become more pronounced when these are discontinued
- 4 A therapeutic trial may establish the diagnosis by using iodine and/or thiouracil because if no improvement follows search for other causes as
 - a Factitious hyperthyroidism
 - b Pheochromocytoma

IV COMPLICATIONS, SEQUELAE AND ASSOCIATED DISEASES

- A GENERAL**—Same as for initial operation, except for greater incidence of¹
- 1 Tetany—2.9 per cent
 - 2 Vocal cord paralysis—14.7 per cent

V TREATMENT

- A COMMENT**—The choice of the following procedures depends on the
- 1 Severity of the case
 - 2 Amount of thyroid tissue
- B MEDICAL**
- 1 Lugol's solution—see 26 \VI B
 - 2 Thiouracil preparations—see 26 \VI D
 - 3 Radioactive iodine—see 26 \VI H
- C ROENTGEN**—see 26 \VI G
- D SURGICAL**—Removal of thyroid remnants may be necessary

VI PROGNOSIS^{2,4}

A COMMENT

- 1 Outcome for permanent cure is less favorable if factors which initiate disorder continue to function
- 2 If cause is inadequate removal of thyroid tissue, results should be same as for subtotal thyroidectomy
- 3 The process may be entirely masked if iodine is administered for first few months postoperatively
- 4 After the introduction of radical thyroidectomies the incidence was lowered
- 5 At present with thiouracil preparations and radical thyroidectomies, no cases have been noted



FIG 204 HYPERSECRETORY DIFFUSE HYPERPLASTIC GOITER Heart in case shown in Figure 203 Note increase in size of heart shadow Roentgenogram was taken 3 months after final operation



FIG 205 NODULAR GOITER FOLLOWED BY GRAVES'S DISEASE ENOPHTHALMOS ATRIAL FIBRILLATION CONGESTIVE HEART FAILURE PROBABLY RHEUMATIC HEART DISEASE Nodular goiter at 22 years of age without symptoms Treated by radium In complete surgical removal Exophthalmos 4 years later Lugol's solution intermittently for 13 years BMR plus 36% Atrial fibrillation apex rate 148 radial 110 BP 160/80 Weight 129 lbs before diabetes 113 lbs afterward Subtotal thyroidectomy followed by pulmonary edema fever and death on second postoperative day Pathologic report multiple colloid adenomatous goiter weight 110 Gm with secondary hyperplasia Heart—375 Gm All chambers dilated Left ventricular capacity twice normal Mitral valve rolled thickened and fibrosed considered grossly incompetent Lungs—frothy pink fluid from all bronchi Lower right lung and entire left lung firm and subcrepitant Liver 1200 Gm Cause of death pulmonary edema It would appear that patient had rheumatic heart disease and mitral regurgitation Hearts of this size in hyperthyroidism usually have some coincidental heart disease This case also suggests the development of Graves's disease upon a previous nodular goiter

SECTION 28

RECURRENT HYPERTHYROIDISM

I DEFINITION

A SUMMARY

- 1 Recurrent hyperthyroidism may be said to exist when the disease returns following a period of apparent cure or remission after subtotal thyroidectomy or any form of therapy
- 2 Similar pattern as primary disorder except it may be more or less severe
- 3 All the data is the same as under persistent hyperthyroidism except as indicated below

II INCIDENCE

A PAST AND PRESENT DATA¹

- 1 In 1016 cases operated before 1927 589 patients were followed from 10 to 20 years
 - a There were 69 single recurrences or 11 per cent
 - b Some patients had 2 or 3 recurrences
- 2 Other reports show an occurrence of less than 1 to 28 per cent with variable follow up periods^{1,2,3,12,14}
- 3 No data is available on large groups operated upon since 1930
- 4 Sufficient time has not elapsed since antithyroid drugs have been prescribed to evaluate this complication after subtotal thyroidectomy

B OCCURRENCE

- 1 Recurrence may take place in
 - a Few months
 - b Twenty years after the first operation
 - c Any year during the individual's life span
- 2 If more than sufficient thyroid tissue is removed at the first subtotal thyroidectomy resulting in a mild myxedema recurrence of this disorder may be postponed if the individual was destined to have it
- 3 Administration of desiccated thyroid

**TABLE 32 RECURRENCE INCIDENCE OF
HYPERSECRETORY HYPERPLASTIC GOITER
(589 Cases of 1016 Surgical Patients
Followed from 10 to 20 Years¹)**

RECURRENCE	NUMBER	PER CENT OF 589 CASES
Once in those living 10 years or more	53	8.99
Once among former persistent cases	13	
Double or triple known among dead before 10 years	7	
Total number of cases	69	11.0
Total recurrent cases are slightly less than the number of recurrences because of double or triple incidences in 7 patients		13.4

following subtotal thyroidectomy might theoretically reduce the stimulus to recurrence¹

III TREATMENT

A MEDICAL

- 1 Lugol's solution
 - a Treatment of choice in mild cases
 - b Disease may be completely alleviated
 - c Myxedema may be produced in rare instances
 - d Thyroid remnants may increase in size although
 - (1) Basal metabolic rate is normal
 - (2) Patient is asymptomatic
- 2 Antithyroid drugs — hyperthyroidism will respond

B ROENTGEN

- 1 Permanent relief of hyperthyroidism by this procedure
- 2 Production of myxedema by roentgen therapy has not cured some cases even when several surgical attempts had failed previously⁶

TABLE 31 OPERATIONS FOR PERSISTENT
HYPERTHYROIDISM

TIME	NO OF CASES	PER CENT
Prior to 1927	1 016	51
1933 1942	3 444	06

Operations done within a 3 year period after first operation. The data reflect the incidence. Approximately 50 per cent of the persistent cases were controlled with iodine.

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- 2 Hurxthal L M Souders C R DePerio J H and Musulin N Ten to twenty year results following subtotal thyroidectomy for primary hyperthyroidism preliminary report on 1016 patients operated upon before 1927. *S Clin North America* 25 651 656 (June) 1945
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FIG 206 HYPERPLASTIC THYROID REMNANTS IN PERSISTENT AND RECURRENT HYPERTHYROIDISM. Tips of each thyroid pole are involved. Patient operated upon when it was not customary to remove the poles. Several operations over a 25 year period. Patient controlled with Lugol's solution when photograph was taken. See Chart 63 for effect of thyroidal which produced myxedema and rebound phenomena when medication was discontinued.

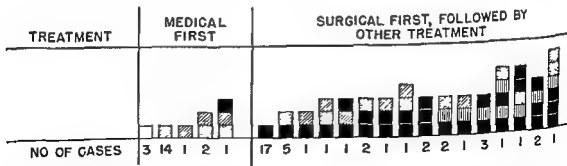
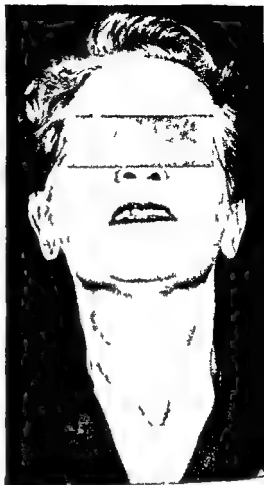


CHART 63 PERSISTENT HYPERSECRETORY DIFFUSE HYPERPLASTIC GOITER. Methods of treatment employed to arrest persistent hyperthyroidism in 1 016 cases operated prior to 1927 (539 were followed 10 to 20 years). Each column represents the sequence of events and the number of cases in which this occurred is indicated beneath each column. When one therapeutic procedure is adjacent to another therapeutic procedure it indicates a persistence of hyperthyroidism.

Open square
Dotted squares

No treatment
Lugol's solution
Vertical lined squares

Black squares
Diagonal lined squares
Recurrence

Operation
Roentgen therapy

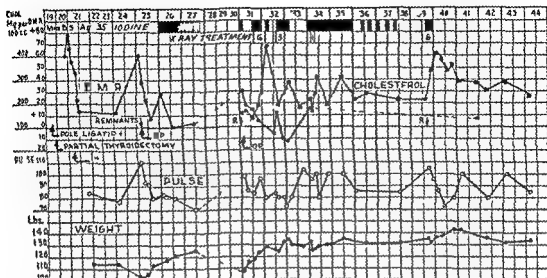


CHART 64 PERSISTENT AND RECURRENT HYPERSECRETORY DIFFUSE HYPERPLASTIC GOITER. Observations on a patient over 25 years necessitating 6 operative procedures roentgen ray therapy and iodine. Temporary myxedema occurred on several occasions but did not require desiccated thyroid. A recurrence of hyperthyroidism was often heralded by the occurrence of paroxysmal auricular fibrillation. In spite of the unusual tendency of the underlying cause to persist the patient is in fairly good health today without any therapy. Vocal cord paralysis or tetany has not developed. This case is representative of a group which fortunately is rare (less than 0.5%).

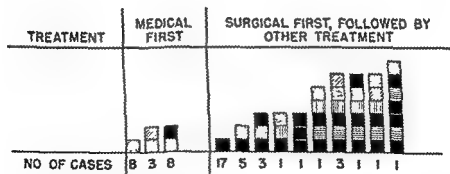


CHART 65 RECURRENT HYPERSECRETORY DIFFUSE HYPERPLASTIC GOITER. Methods of treatment employed to arrest recurrent hyperthyroidism in a group among 1,016 cases operated upon prior to 1927. 589 of which were followed 10 to 20 years. Each column shows the sequence of events and the number of cases in which this occurred is indicated beneath each column. When one therapeutic procedure is adjacent to another therapeutic procedure it indicates a short interval (i.e., months) of persistent hyperthyroidism between—as opposed to longer intervals when indicated as below.

Dotted Lugol's solution Vertical lined Recurrence
Black Operation Horizontal lined Persistence
Diagonal lined Roentgen therapy

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- 13 Troell A Recurrent goiter from a surgical point of view *Acta chir Scandinav Suppl.* 92 1 62 1944
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FIG 20/ RECURRENT HYPERSECRETORY DIFFUSE HYPERPLASTIC GOITER Age 29 BMR plus 78% Subtotal thyroidectomy Weight increased from 113 to 133 lbs BMR's since operation were from minus 12% to plus 1% Note apparent decrease in exophthalmos which was probably due to loss of lid retraction (Left) Before operation (Center) Three months after operation (Right) Ten years later with recurrence of hyperthyroidism

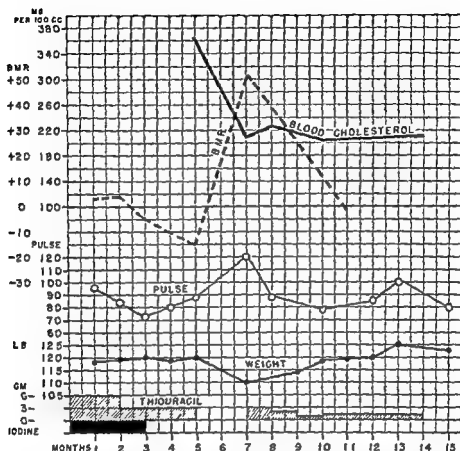


CHART 67 RECURRENT HYPERSECRETORY DIFFUSE HYPERPLASTIC GOITER Effect of substitution of thiouracil on iodized patient with recurrent hyperthyroidism Temporary myxedema produced Note rebound on discontinuing thiouracil as well as iodine (10 minims daily) and its effectiveness when resumed (Hurxthal L W Myxedema and its various causes *J Clin North America* 25 65, 6:1)

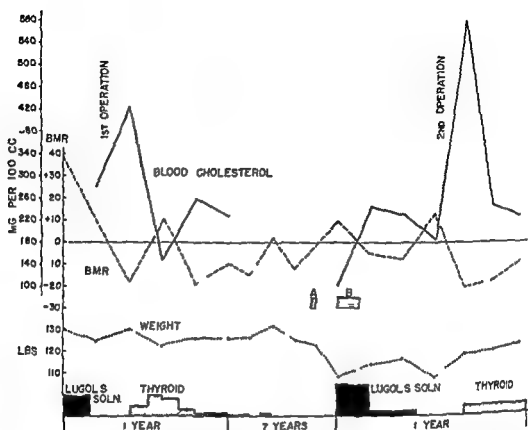


CHART 66 RECURRENT HYPERSECRETORY DIFFUSE HYPERPLASTIC GOITER AFTER POST OPERATIVE MYXEDEMA Nine year observations on a patient with Graves disease who developed postoperative myxedema and gradually a recurrence of thyroid function to the point of hyperthyroidism. A second operation and conservative removal of hyperplastic remnants again resulted in clinical myxedema necessitating the use of desiccated thyroid. Three years later thyroid medication was unnecessary and the patient appeared to have normal thyroid function. Recurrence is possible in view of previous experience.

A Size of thyroid remnant when first palpated

■ Two years later approximately 4 times size of A

Desiccated thyroid (U.S.P.) dosage varied from $\frac{1}{4}$ to 4 gr daily. Lugol's solution—3 to 30 minims daily (Hurxthal L. M. Myxedema and its various causes S. Clin. North America 25: 657-671)



FIG 208 APATHETIC HYPERTHYROIDISM
Age 59 Apathetic hyperthyroidism with de
compensation Auricular fibrillation and
ascites Patient lost 11 lbs of water pre
operatively Weight 86 lbs BMR plus 68%
RBC 3 560 000 Hgb 58%

SECTION 29

APATHETIC HYPERTHYROIDISM¹⁻⁶

SYNONYMS Masked hyperthyroidism, *Forma frusta*

I DEFINITION Hyperthyroidism from hypersecretory nodular or hyperplastic goiter in which the usual characteristics are not evident

II APPEARANCE Apathetic

III AGE Usually older group, but may be seen in the young

IV SEX Predominantly females

V PHYSICAL STATUS

A SKIN Often diffuse tanning, sweating is not excessive
B EYES Exophthalmos appears less frequent
C PULSE May be proportionate or disproportionate to elevation in basal metabolic rate, auricular fibrillation

VI LABORATORY DATA Basal metabolic rate slightly or moderately elevated

VII PATHOLOGIC PHYSIOLOGY

A SUMMARY

- 1 Patients may represent end result of severe, activated hyperthyroidism
- 2 Entity may show loss of
 - a Tissue (negative nitrogen and calcium balance)
 - b Adrenocortical anabolic effects
 - c Ability to react to an excess of thyroid hormone
- 3 Associated diseases
 - a Thyrocardiac disease
 - b Diabetes mellitus

VIII TREATMENT—see 26 \VI

REFERENCES

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3 Secondary factors⁷

- a Age
- b Coincidental heart disease

4 Inability of the heart to maintain circulatory needs of an increased metabolic rate results in failure even though circulatory rate may be normal

- c Cough
- d Tachycardia
- e Cyanosis
- f Edema
- g Epigastric distress

VIII PATHOLOGY (see 26 \)

A HEART

- 1 Hypertrophy may be⁸
 - a Slight
 - b Moderate
- 2 Dilatation if death is due to cardiac failure⁹
- 3 Histologic changes
 - a Nothing specific¹⁰
 - b Brown atrophy and necrosis rarely if ever seen since iodine therapy⁶

IX PATHOLOGIC PHYSIOLOGY

A EFFECT OF HYPERTHYROIDISM ON THE CARDIOVASCULAR SYSTEM

- 1 Blood flow increased (see Charts 68 and 69)
 - a Greater metabolic demands of the tissues and cardiac muscle from direct action of thyroid hormone increase the heart rate independently¹⁰
 - b Peripheral vascular dilatation acts similar to an arteriovenous shunt and more blood flow to thyroid gland adds further to this effect
- 2 Pulmonary pressure is increased which may
 - a Cause a prominent pulmonary arc
 - b Result due to a decreased peripheral and pulmonary vascular resistance producing a piling up effect in the pulmonary artery¹⁰
- 3 Cardiac findings—see 26 \ I A 4

X SYMPTOMATOLOGY

A HYPERTHYROIDISM—see 26 \ II

B CARDIOVASCULAR

- 1 Variable depending on
 - a Degree of decompensation
 - b Severity and duration of disease
 - c Management
- 2 General
 - a Dyspnea
 - b Orthopnea

XI DIAGNOSIS

A HISTORY

- 1 Important in clinical evaluation
- 2 Weight loss in spite of adequate caloric intake

B PHYSICAL STATUS

- 1 It may be difficult to diagnose hyperthyroidism in presence of overshadowing heart symptoms
- 2 Skin
 - a Warm and moist in contrast with dryness in other types of heart disease
 - b Pigmentation may be beyond that which comes with contraction of the skin
- 3 Stare is present even though exophthalmos is absent
- 4 Thyroid gland may be
 - a Enlarged and firm
 - b Normal in size and consistency
 - c Adenomatous and completely substernal which may be detected by roentgenograms of trachea (see 26 VIII F 1)
- 5 Pulse
 - a Rate if not irregular is above normal except occasionally in men
 - b Pressure increased
- 6 Tremor not diagnostic

C LABORATORY DATA—Basal metabolic rate is elevated with

- 1 Congestive failure
- 2 Cardiac compensation
- 3 Aortic stenosis (complicated)

XII DIFFERENTIAL DIAGNOSIS

A MITRAL STENOSIS—Description

- 1 Rumbling diastolic murmur
- 2 Presystolic crescendo culminating in a booming first sound

B HYPERTENSIVE HEART DISEASE WITH CONGESTIVE FAILURE

- 1 While an elevated diastolic pressure may be present in hyperthyroidism it is rare

SECTION 30

THE THYROCARDIAC PATIENT

I DEFINITION

Individuals with hyperthyroidism who have congestive heart failure with regular rhythm, auricular fibrillation or flutter, which are established and not paroxysmal patients with coincidental heart disease without the above specifications not included (see Figs 209, 211 and 212)

II APPEARANCE

Many of the characteristic findings of hyperthyroidism are not evident

III AGE

Average over 50 years 60 per cent over 60, 20 per cent over 50 20 per cent under 50

IV SEX

Females predominate

V PHYSICAL STATUS

A GENERAL

Those found in hyperthyroidism (see 26 VI)

B THYROID

Enlarged, but frequently quite small, firm normal (less than 2%) in size and consistency adenomatous goiter may be partially or completely substernal, but the latter is rare

C CARDIAC DECOMPENSATION

Edema (may be concealed), liver is enlarged and/or tender, neck veins engorged orthopnea cyanosis

VI ROENTGENOGRAPHIC FINDINGS

Large heart shadow in some thyrocardiac patients is the result of dilatation from congestive heart failure, return to normal size is common in the majority of patients¹⁰

TABLE 33 COEXISTENT CARDIOVASCULAR DISEASE IN THYROCARDIACS (Total—469 Cases⁷)

	CASES No or
Hypertension noted postoperatively	36
Hypertension (160/90 or more preoperatively)	35
Mitral stenosis (not including patients with apical systolic murmurs and rheumatic history)	27*
Coronary artery disease (clinical)	10
Aortic regurgitation (rheumatic)	2
Aortic stenosis	1
Miscellaneous (congenital acute rheumatic carditis pericarditis)	6

VII ETIOLOGY⁷

A CONGESTIVE HEART FAILURE

- 1 Primary cause—hyperthyroidism
 - a There is a greater incidence of cardiac decompensation in patients with toxic adenoma than diffuse hypersecretory hyperplastic goiter³
 - b Among 7,363 cases of hyperthyroidism, congestive heart failure occurred in 3.7 per cent (around 20.2 per cent in literature)⁸
- 2 Auricular fibrillation or flutter
 - a Precipitating cause in 85 per cent
 - b Heart failure is four times as common in thyrotoxic patients with established auricular fibrillation as with normal rhythm
 - c The incidence for both among 7,363 cases of hyperthyroidism was 5.7 per cent⁸

* In 444 cases of hyperthyroidism without congestive heart failure or auricular fibrillation the number of patients with mitral stenosis was 21 showing only slightly increased incidence in the thyrocardiac group

- 3 Secondary factors[†]
 - a Age
 - b Coincidental heart disease
- 4 Inability of the heart to maintain circulatory needs of an increased metabolic rate results in failure even though circulatory rate may be normal

VIII PATHOLOGY (see 26 V)

A HEART

- 1 Hypertrophy may be^{3 5 11 17}
 - a Slight
 - b Moderate
- 2 Dilatation if death is due to cardiac failure³
- 3 Histologic changes
 - a Nothing specific¹⁶
 - b Brown atrophy and necrosis rarely if ever seen since iodine therapy⁶

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 - b Result due to a decreased peripheral and pulmonary vascular resistance producing a piling up effect in the pulmonary artery¹⁰
- 3 Cardiac findings—see 26 VII A 4

X SYMPTOMATOLOGY

A HYPERTHYROIDISM—see 26 VII

B CARDIOVASCULAR

- 1 Variable depending on
 - a Degree of decompensation
 - b Severity and duration of disease
 - c Management
- 2 General
 - a Dyspnea
 - b Orthopnea

- c Cough
- d Tachycardia
- e Cyanosis
- f Edema
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 - b Pressure increased
- 6 Tremor not diagnostic

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- 2 Cardiac compensation
- 3 Aortic stenosis (compensated)

XII DIFFERENTIAL DIAGNOSIS

A MITRAL STENOSIS—Description

- 1 Rumbling diastolic murmur
- 2 Presystolic crescendo culminating in a booming first sound

B HYPERTENSIVE HEART DISEASE WITH CONGESTIVE FAILURE

- 1 While an elevated diastolic pressure may be present in hyperthyroidism it is rare

- 2 Left ventricular hypertrophy may be marked
- 3 Decision must rest on evaluation of other signs and/or symptoms
- 4 Basal metabolic rate may also be elevated (see 44 VII E 1)

C MISCELLANEOUS

- 1 Hyperthyroidism may occur with any type of cardiovascular disease capable of ending in congestive failure
- 2 Paroxysmal auricular fibrillation or flutter that develops in the presence of coincidental heart disease (especially mitral stenosis) may cause
 - a Respiratory distress
 - b Acute decompensation

XIII TREATMENT

A GENERAL—see 26 XVI

B ACUTE CONGESTIVE HEART FAILURE WITH THYROID CRISIS

- 1 Medications—dosage
 - a Digitalis preparations
 - (1) Initial (intravenous)—calculated per 15 lbs of body weight in patients who have not had this medication for 2 to 3 weeks previously

(a) Digalen	1 cc
(b) Digoxin	0.1 mg
(c) Digatoxin	0.02 mg
(d) Lantoside C	0.4 mg
 - (2) Procedure—amounts as above repeated in 6 hrs if needed and tolerated
 - (3) Maintenance (oral)

(a) Digitalis	1.5 gr
(b) Digoxin	0.5 mg
(c) Digatoxin	0.1 mg
(d) Lantoside C	1.0 mg
 - b Strophantin (ouabain)
 - (1) Intravenous 0.5 mg initially if no digitalis taken by patient for 10 days previously
 - (2) Procedure 0.1 mg every half hour until ventricular rate is below 80/min
 - (3) Maximum No more than 1 mg should be given in 24 hrs

c Mercurial diuretics

- (1) Indication—marked edema
 - (2) Dosage—1 to 2 cc intravenously
 - d Morphine— $\frac{3}{8}$ to $\frac{1}{4}$ gr hypodermically, every 3 hrs as necessary
- 2 Management (see 26 XVI M 1)
 - a Restrict fluids to 3 000 cc. per day if given intravenously, administer very slowly
 - b Salt should not be used
 - c Venesection (400 to 600 cc) indicated, if cyanosis is not relieved by oxygen

- 3 Result—unless severity of hyperthyroidism cannot be abated, acute congestive failure can be adequately eliminated

C CHRONIC CONGESTIVE HEART FAILURE

- 1 Medication (see Charts 70 73)
 - a Digitalize patient within 24 to 72 hrs (see above)
 - b Acid salts such as ammonium chloride
 - (1) Useful
 - (2) Dosage—15 gr q.i.d. orally
 - c Theophyllin or mercurial diuretics if needed
- 2 Management (see 26 XVI)
 - a If cyanosis is not relieved by oxygen venesection (400 to 600 cc) indicated
 - b Diet
 - (1) Salt free or no added salt
 - (2) Acid ash
- 3 Results
 - a Mild to moderate congestive failure will cease with
 - (1) Bed rest, occasionally
 - (2) Bed rest plus iodine sometimes
 - (3) Antithyroid drugs, usually
 - b It is desirable to treat both hyperthyroidism and congestive failure simultaneously

D AURICULAR FIBRILLATION OR FLUTTER (see Charts 70 and 75)

- 1 Quinidine
 - a Indication—if auricular fibrillation persists and when the patient has been properly prepared with an antithyroid drug it is not likely to recur
 - b Dosage
 - (1) Oral initially 3 gr t.i.d. p.c. for one day

- (2) Procedure If not effective, 6 gr are given tid pc until paroxysmal auricular fibrillation stops, medication discontinued if any unpleasant symptoms arise

(3) Intravenous Rarely needed

- 2 Morphine only can be used to quiet patient if there is no cardiac embarrassment

E TOTAL THYROIDECTOMY FOR HEART DISEASE^{1 9}

- 1 Practice abandoned
 - a There may be rare circumstances when it might still be applied
 - b Best results in chronic heart failure from rheumatic heart disease or angina pectoris^{1 13}
- 2 Lessons learned
 - a Complete ablation is necessary to produce myxedema
 - b Myxedema eventually causes a poorer cardiac function, thus a return of original signs and symptoms
- 3 The excellent theory that desiccated thyroid can be given after total ablation to prevent full blown myxedema but at the same time to relieve cardiac symptoms has not been proved sufficiently from actual experience to warrant its continued use
- 4 Radioactive iodine is now being tried

XIV PROGNOSIS

A MORTALITY OF THYROID SURGERY IN THYROCARDIACS

- 1 Prethiouracil era (1922 to 1941)—614 cases (6.6%)
- 2 Thiouracil era (1943 to 1947)—none

TABLE 34 STATUS OF 469 OPERATED CASES (1922 TO 1941, AT 1942 FOLLOW UP¹)

Known alive	306
Excellent	201
Good	100
Poor	5
Known dead	165
Untraced	143
Postoperative myxedema	14 (2.9%)
Persistent auricular fibrillation (in good group of known alive)	84 (27%)

B LIFE EXPECTANCY AND OUTCOME

- 1 After successful surgery, 50 per cent of normal expectancy (based on 469 cases followed 10 to 15 years¹)
- 2 Persistent auricular fibrillation
 - a Life expectancy in thyrocardiacs does not decrease (see Chart 73)¹¹
 - b After subtotal thyroidectomy, may subside spontaneously
- 3 Recurrent congestive heart failure is rare without
 - a Recurrence of hyperthyroidism
 - b Severe coincidental heart disease
- 4 Angina may be entirely relieved after subtotal thyroidectomy

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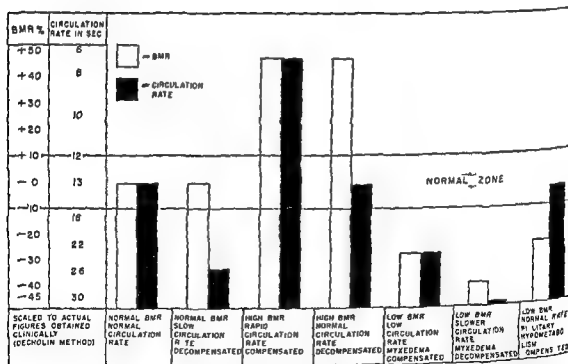


CHART 68 CIRCULATION RATES IN VARIOUS CONDITIONS WITH ABNORMAL METABOLIC RATES Schematic relationship between circulation rate and BMR in normal hyperthyroid myxedematous and hypopituitary persons. The circulation time is increased in hyperthyroidism and when the heart cannot keep up with the demands of a high BMR cardiac failure develops eventually (Hurxthal L M Frank Howard Lahey—*Birthday Volume Springfield Ill Baltimore* pp 245 269)



FIG 209 THYROCARDIAC PATIENT (*Top*) Age 51 female Hyperplastic goiter auricular fibrillation and severe congestive heart failure with anasarca Duration of goiter 17 years Symptoms of hyperthyroidism 10 years Weight 219 lbs BMR plus 45% After preoperative preparation weight 142 lbs RBC 3.2 million Hgb 54% NPN 34 mg % blood chlorides 495 mg % After diuresis RBC 4.0 to 5.6 million Hgb 85% serum protein 9.1 and 8.9 Gm % blood chlorides 443 mg % (*Bottom*) Three months after last operation She had a pole ligation and 2 hemithyroidectomies Edema free no dyspnea Weight 146 lbs Pulse 54 (auricular fibrillation) BMR minus 5% Multiple stage operations are unnecessary with thiouracil treatment In cases with such severe anasarca diuretics and digitalis should still be employed while waiting for the effect of anti thyroid drugs

FIG 210 HEART SHADOWS IN THYROCARDIAC PATIENT (See also Chart 71) Graves disease of 17 years duration in a male with auricular fibrillation and congestive heart failure (Left) Roentgenogram of chest on admission to hospital (Right) Eighteen days later, and before operation (Hurxthal L M Heart failure and hyperthyroidism with special reference to etiology, Am Heart J 4 103 108)

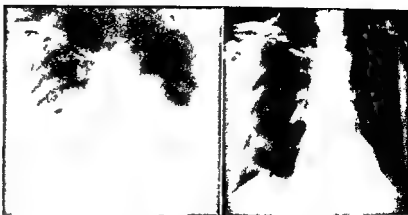


FIG 211 THYROCARDIAC PATIENT Congested neck veins in a thyrocardiac Nodular goiter auricular fibrillation hyperthyroidism and congestive heart failure



FIG 212 THYROCARDIAC PATIENT Age 51 female with severe hyperthyroidism showing emaciation exophthalmos and enlarged thy

roid Congestive heart failure auricular fibrillation and orthopnea BMR plus 49% Weight 94 lbs Weight loss 50 lbs in 2 years Patient survived bilateral pole ligation Died suddenly 2 days postoperatively with fever rising to 105 F Postmortem examination revealed a heart weighing 320 Gm dilated especially on right side Pericardium obliterated by numerous delicate fibrous adhesions Myocardium flabby and brownish color showed a few large fibers and slight amount of granular precipitate in interstitial tissue Adrenals had diminution of cortical lipid Lymph glands considered enlarged Thymus not found Lungs revealed no foci of pneumonia mucopurulent secretion in bronchi Liver 1080 Gm appeared normal except for indistinct lobules Many cells revealed vacuolization No necrosis lobules smaller than normal Remaining lobe of thyroid weighed only 15 Gm majority of acini lined with flattened epithelium filled with colloid Numerous papillary ingrowths with columnar epithelium Death was assigned to heart failure which was probably true in view of its suddenness The high fever and the purulent bronchial secretion are frequent findings in those dying of thyroid storm The pericarditis rather than hyperthyroidism was probably the cause of such great hypertrophy in the absence of valvular disease and hypertension

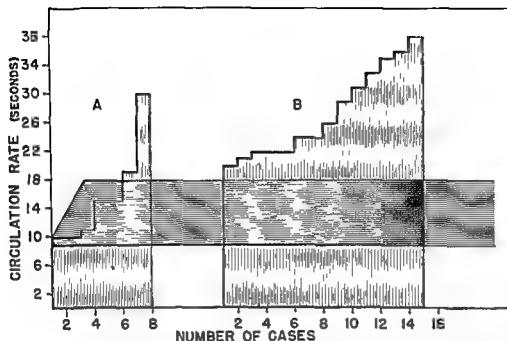


CHART 69 CIRCULATION RATES IN CONGESTIVE FAILURE Normal zone shown by horizontal shaded area. (A) In hyperthyroid patients with congestive failure. (B) In nonhyperthyroid patients with congestive failure. Note normal values in all cases of hyperthyroidism except 2 patients (7 and 8) in whom there was severe congestive failure (i.e. anasarca hydrothorax etc). Most hyperthyroid patients without congestive failure have circulation rates below 12 sec and occasionally as low as 6 sec. See Chart 68 for relationship between BMR and circulation rate in hyperthyroidism (arm tongue with decholin) (Hurxthal L. M. and Claiborne T. S. Unpublished data.)

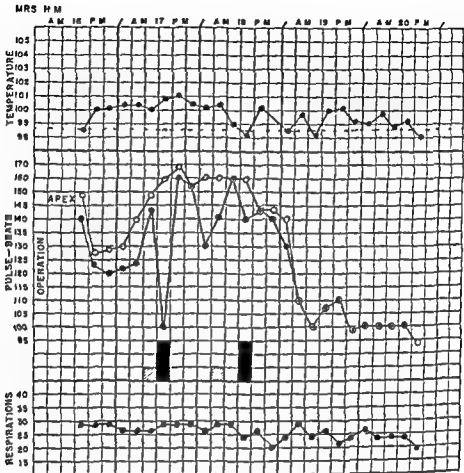


CHART 70 DIGITALIS THERAPY IN PAROXYSMAL AURICULAR FIBRILLATION
 Effect in intravenous digitalis (digalen) on paroxysmal auricular fibrillation occurring after subtotal thyroidectomy. Hospital chart. Ordinarily paroxysmal auricular fibrillation causes no respiratory difficulty but in this case a patent ductus arteriosus was present and patient was given digitalis because of orthopnea.
 Diagonal lined areas = 3 gr of digitalis leaf Solid areas = 3 ampules of digalen

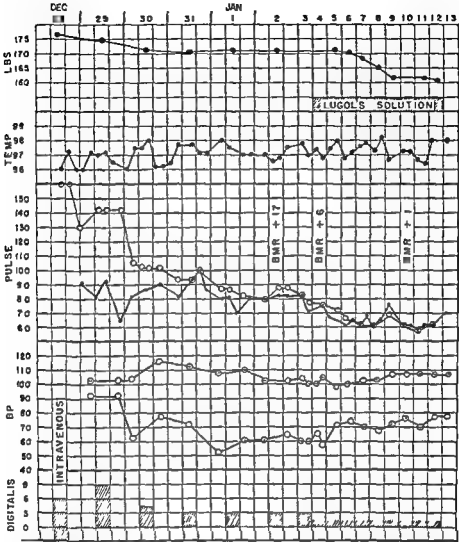


CHART 71 THYROCARDIAC—EFFECT OF DIGITALIS LUGOL'S SOLUTION AND BED REST (See also Fig 210) Chart of patient male age 42 with exophthalmic goiter and severe congestive heart failure. No pulse or BP could be obtained on admission to hospital. Note drop in heart rate on digitalis and rest alone. Lugol's solution given on eighth day. Note sudden loss of 10 lbs of edema following its use. Metabolism test was not done on admission. His pulse later became regular before operation and without quinidine. The patient's critical condition on admission was the result of heart failure rather than thyroid toxicity although the latter was the cause of the former. There was a marked reduction in the size of the cardiac shadow after recovery from failure and after auricular fibrillation had ceased (Hurxthal L M The heart in hyperthyroidism New England J Med 208 528 541)

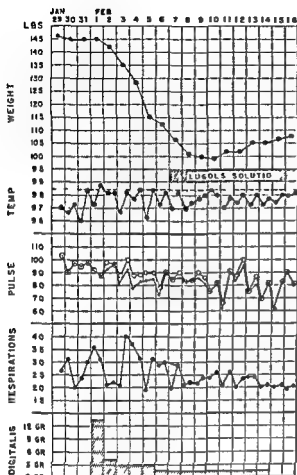
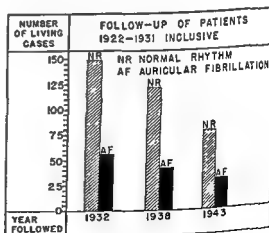


CHART 72 (Left) THYROCARDIAC—EFFECT OF DIGITALIS AND BED REST Hospital chart of a woman age 30 with nodular goiter hyperthyroidism, rheumatic heart disease with mitral regurgitation and slight stenosis Auricular fibrillation present Note weight remained level with rest in bed alone Digitalis given by mouth was followed by a diuresis of 35 lbs Note continuation of diuresis when Lugol's solution was begun and then a gain of real weight (nitrogen retention?) amounting to 8 lbs The pulse rate here was not exceptionally fast BMR on admission plus 48% Patient was operated upon in 2 stages Auricular fibrillation ceased patient gained 37 lbs and fully recovered (Hurxthal L M The heart in hyperthyroidism New England J Med 208 538 541)

CHART 73 (Right) THYROCARDIAC PATIENTS WITH NORMAL RHYTHM AND AURICULAR FIBRILLATION AFTER OPERATION Ratio of thyrocardiac patients having normal rhythm and persistent auricular fibrillation and the effect on rate of survival over period of 10 to 20 years It appears that auricular fibrillation does not influence survival rate in this group In most instances patients with auricular fibrillation received digitalis (Lahey F H Hurxthal L M and Driscoll R E Thyrocardiac disease a review of 614 cases Ann Surg 118 681 691)



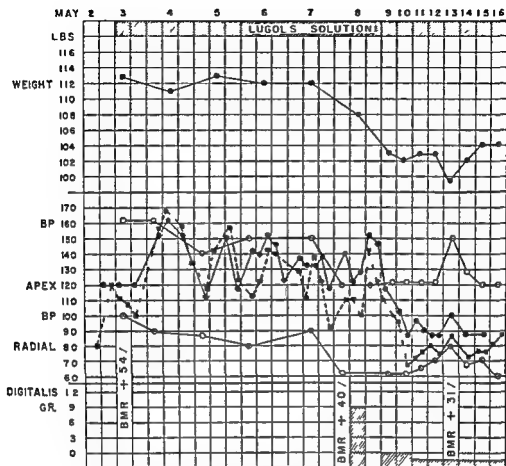


CHART 74 THYROCARDIAC—THERAPY OF CONGESTIVE FAILURE Effect of bed rest and Lugol's solution on patient with hypersecretory hyperplastic goiter and congestive heart failure Note that there was very little change in weight until digitalis was given However this may be due to a combination of retention of fluid for anabolic processes with actual reduction of cardiac and other edema from the effects of iodine Yet the rapid drop in heart rate with digitalis shows its effectiveness Postmortem examination of heart showed no abnormality Weight 300 Gm (This = a hospital chart and it is obvious that the initial observations on apex and radial pulse were in error)

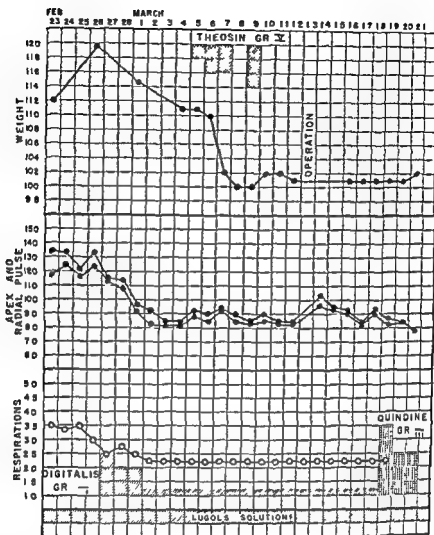


CHART 15 THYROCARDIAC—THERAPY INCLUDING QUINIDINE SULFATE
 Chart showing results of bed rest digitalis theosin and quinidine in a case of toxic adenomatous goiter with auricular fibrillation and congestive heart failure Female age 55 BMR plus 25% Note increase in edema on Lugol's solution and bed rest then diuresis and slowing of pulse after digitalis (each square represents 3 gr digitalis leaf) Further diuresis after theosin (each square represents 5 gr orally) Pulse became regular on third day of quinidine therapy (each square represents 3 gr quinidine sulfate orally) (Hurxthal L M The heart in hyperthyroidism New England J Med 208 538 541)

SECTION 31

HYPERTHYROIDISM AND DIABETES MELLITUS

I DEFINITION

A patient with characteristics of hyperthyroidism and diabetes mellitus the significant features of this combination only are mentioned here otherwise refer to specific chapters

II AGE

Average age of onset of diabetes in diffuse hypersecretory hyperplastic goiter is 41.5 adenoma with hyperthyroidism is 50.2³

III LABORATORY DATA

A URINE	Normal or glycosuria ^{1 5 6 7}
B BLOOD SUGAR (fasting)	Normal or increased ^{1 5 6 7}
C GLUCOSE TOLERANCE TEST	Curve is not dependent on severity of case impaired function in 66 per cent of all cases of hyperthyroidism
D BASAL METABOLIC RATE	Increased

IV ETIOLOGY

A FACTORS—It is not known definitely whether or not hyperthyroidism causes diabetes

V PATHOLOGIC PHYSIOLOGY

A LIVER

- 1 Glycogen content is poor because of failure to convert or store glucose for tissue demand is so great
- 2 Damage is not chief factor in hyperglycemia

B RENAL THRESHOLD

- 1 Low in patients with hyperthyroidism
- 2 Severity of the disease bears no relationship
- 3 Glycosuria is found in
 - a Mild or severe cases with or without diabetes
 - b Postoperative patients unless adequately controlled with diet and/or insulin

C PANCREAS

- 1 Insulin brings improvement by
 - a Glycogen storage
 - b Decrease in ketone bodies
 - c Protein sparing action
- 2 Hyperglycemia in hyperthyroidism
 - a Unrelated to severity of disease
 - b Incidence—0.5 to 90.0 per cent (average 18.31%)^{1 5 6 7}

TABLE 35 INCIDENCE^{1 5 7}

CASES	RANGE PER CENT	AVERAGE PER CENT
Hyperthyroidism discovered in diabetics	0.97-3.0	1.68
Diabetes mellitus found in hyperthyroidism	0.5-4.3	2.31
	PER CENT GLYCOSURIA (Incidence—1.0 to 38.6)	PER CENT DIABETES
Hypersecretory diffuse hyperplastic goiter	38.6	1.7 and 2.5
Adenomatous goiter with secondary hyperthyroidism	27.7	4.3 and 5.6

VI TREATMENT

A GENERAL—see 26 VII

B RESULTS AFTER SUBTOTAL THYROIDECTOMY

- 1 Carbohydrate tolerance improves if not then
 - a Diabetic management is inadequate
 - b Infection may be present
 - c Other complications should be sought
- 2 Diabetes mellitus may develop after surgery due to
 - a Insufficient removal of thyroid tissue
 - b Specific factors that can produce it

SECTION 32

HYPERTHYROIDISM AND PREGNANCY

I DIAGNOSIS

A SUMMARY

- 1 Hyperthyroidism may develop at any stage of pregnancy
- 2 Last trimester
 - a The diagnosis of this complication aside from physical signs, will require an increase of at least plus 30 per cent or more in the basal metabolic rate^{19 20 21}
 - b Normally there is about a 25 per cent increase (falls to normal after parturition) which is due to the
 - (1) Fetal^{1 20 23}
 - (a) Thyroid (may be functioning)^{29 30}
 - (b) Size
 - (2) Maternal tissue changes to a lesser degree²³
- 3 Vomiting of hyperthyroidism may be mistaken for hyperemesis gravidarum¹³
- 4 Conception rarely occurs in hyperthyroid patients^{21 28 30}

- 2 Hyperthyroidism or cretinism rarely occurs^{17 44}
- 3 Goiter may develop
- 4 Thiouracil in milk is harmful to new born rats²³

III TREATMENT

A MANAGEMENT

- 1 Hyperthyroidism is treated first and not the pregnancy
- 2 Induced abortion is contraindicated^{7 15 22}
 - a Hyperthyroidism is not relieved
 - b Thyroid crisis may result
- 3 Antithyroid drugs and iodine in preparation for subtotal thyroidectomy (see 26 XVI E)³⁰
 - a Management same as for nonpregnant women
 - b Subtotal thyroidectomy is safe in first two trimesters none reported in last trimester
 - c Results—effective—10 16 — 8 4
- 4 Antithyroid drugs without thyroidectomy
 - a Basal metabolic rate should be kept around plus 20 to plus 30 per cent until term
 - b Careful observation for thyroid deficiency (i.e. hypercholesterolemia)
 - c Program as outlined below may be desirable to prevent fetal loss
 - d Patient should not nurse while taking antithyroid drugs
- 5 After subtotal thyroidectomy during pregnancy, the following program seems justified until term
 - a Desiccated thyroid—1 to 2 gr orally daily
 - b Lugol's solution—5 drops orally daily in chocolate milk after meals
 - c Stilbestrol (see 60 II J) if evidence of
 - (1) Threatened abortion
 - (2) Toxemia
- 6 Premature delivery or cesarean section has been performed before antithyroid drug era not recommended now^{3 14 4}

TABLE 36 INCIDENCE^{4 7 8 9 10 17 21 31 34 39}

	PERCENTAGE
Pregnancy complicated by hyperthyroidism	0.5 to 1.4
Hyperthyroidism complicated by pregnancy	0.4 to 0.6

II COMPLICATIONS

A MATERNAL

- 1 Abortion or premature delivery (54 5%)^{18 30}
- 2 Difficult and prolonged labor taxes the heart
- 3 Postpartum hemorrhage^{8 9 43}
- 4 Tracheal compression if nodular goiter
- 5 Thyroid crisis during
 - a Labor
 - b Postpartum
- 6 Toxemia of pregnancy²

B FETAL

- 1 Infant's health is normal^{25 3 37 45}

TABLE 37 OUTCOME OF 16 PREGNANT WOMEN TREATED WITH ANTITHYROID DRUGS, IODINE AND SUBTOTAL THYROIDECTOMY DURING FIRST TWO TRIMESTERS*

NO OF CASES	MOTHERS	BABIES
11	Normal deliveries	Normal
1	Abortion at 5 months	Died
1	Premature delivery	Stillbirth
1	Premature delivery	Died 8 hrs later
1	Eclampsia	Stillbirth at term
1	Cesarean section	Died 4 hrs later

IV PROGNOSIS

A HYPERTHYROIDISM (untreated)

- 1 Some patients may^{a, b, c}

- a Improve in latter months of pregnancy or postpartum
- b Become worse
- c Have other pregnancies without any difficulty

- 2 The majority do fairly well with proper management

- 3 "Latent" or unrecognized hyperthyroidism may become manifest at parturition

B PREGNANCY (treated or untreated)

- 1 Normal^{1 10 25 3 3 45}
- 2 Abortion—see Table 37
- 3 Stillbirth—see Table 37^{2 1 10 21 40}
- 4 Fetal goiter
- 5 Thyroid deficiency in fetus^d

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SECTION 33

EXOPHTHALMIC SYNDROME

I DEFINITION

The presence of unexplained unilateral or bilateral exophthalmos with little or no evidence of hyperthyroidism or enlargement of the thyroid gland. If progressive to an undesirable degree, exophthalmos is termed malignant.

II APPEARANCE

Normal looking individual except for unilateral or bilateral prominence of the eyes and usually without enlargement of the thyroid gland (see Figs 213 and 214).

III AGE

Variable

IV SEX

Males predominate in ratio of 4:1,¹⁵ malignant postoperative exophthalmos develops more often in men.

V PHYSICAL STATUS

A EYES

Exophthalmos of variable degree. Unilateral or bilateral may be complicated by conjunctivitis, excessive lacrimation (epiphora), diplopia, external ophthalmoplegia, periorbital edema, chemosis of conjunctivae (excessive edema of ocular conjunctiva), acute swelling of lids, blepharitis, corneal ulcer, keratinization of conjunctivae, orbital infection, blindness from optic atrophy or papilledema, panophthalmitis.

B THYROID

Normal or slightly enlarged.

C OTHER SIGNS

May be present as in hyperthyroidism or none at all, except the above.

VI LABORATORY DATA

A URINE

Labeled (radioactive) iodine excreted in greater amounts than in primary hyperthyroidism.¹⁶

B BLOOD CHEMICAL ANALYSES

1 Cholesterol (plasma)

Normal

2 Iodine (protein bound)

Normal.²⁰

C BASAL METABOLIC RATE

Normal, decreased or slightly increased.

D URINARY HORMONE ASSAY

Thyrotropic hormone (TSH) excreted in active and in active form.²⁷⁻²⁹ Level in blood may be high.⁷

VII ETIOLOGY

A UNKNOWN

B POSSIBLY SAME FACTORS AS IN HYPER THYROIDISM—see 26 IX

VIII PATHOLOGY

A THYROID

1 Normal

2 Same as in mild hyperthyroidism—see 26 X A 1, B 1

B EYES

1 Gross

- a Extrinsic muscles are swollen in some cases from 3 to 8 times the normal size, causing increased intra orbital tension.²²
- b Orbital fat markedly increased.²⁹
- 2 Microscopic—muscles show
 - a Edema
 - b Round cell infiltration
 - c Loss of structure
 - d Fragmentation
 - e Hyalinization
 - f Fibrous tissue in increased amounts

- g Pallor
- h Rubbery hardness
- i Lymphorrhages (infiltrations of lymphocytes with some plasma and endothelial cells)⁹

IX PATHOLOGIC PHYSIOLOGY

A GENERAL (see Chart 50, p 479)

- 1 The underlying conditions leading to the pathologic and physiologic changes are unknown
- 2 Rare as a primary disorder
- 3 Development frequently following therapeutic arrest of hyperthyroidism
- 4 Occurrence years later is possible with out recurrence of hyperthyroidism
- 5 Malignant exophthalmos is found in less than 1 per cent of all cases

B THYROID GLAND

- 1 Exophthalmos is found in postoperative cases of hyperthyroidism, therefore thyroid gland is not the primary factor⁸
- 2 Idiopathic exophthalmos occurs in the absence of thyroid disease

C THYROTROPIC HORMONE

- 1 Excessive amounts of this hormone in blood and urine may or may not cause exophthalmos³
- 2 Spontaneous myxedema does not produce this syndrome in spite of increased amounts of TSH
- 3 A balance normally exists between TSH and thyroid hormone in relation to water storage

- a If this mechanism is altered the orbit may be affected because of its structure

- b Significance to edema of ocular muscles debatable

- 4 Injections of TSH (also anterior pituitary extracts) in various animals^{10 11}

- a Exophthalmos is produced in many species regardless of
 - (1) Thyroidectomy (more severe and readily produced)
 - (2) Hypophysectomy
 - (3) Sympathectomy

- b Younger animals develop exophthalmos more often

- Thyrotropic induced exophthalmos in guinea pigs becomes worse during

a refractory period especially in those with low basal metabolic rates¹⁰

- d Fat globules are produced in⁸

- (1) Muscles
 - (a) Ocular
 - (b) Cardiac
 - (c) Skeletal
- (2) Liver
- (3) Epithelial cells
- (4) Phagocytes in
 - (a) Lungs
 - (b) Spleen
 - (c) Lymph nodes

e Muscles

- (1) Pale
- (2) Edematous
- (3) Lymphocytic infiltration
- (4) Scar tissue

f Increase in

- (1) Lipoids (plasma)
- (2) Acetone (blood)

D SYMPATHETIC SYSTEM

- 1 Role is not known in this syndrome
- 2 In humans cervical sympathetic stimulation causes no protrusion of eye balls except when exophthalmos is already present¹⁰

E DRUGS PRODUCING EXOPHTHALMOS

- 1 Potassium thiocyanate given for hypertension
- 2 Sulfathiazole (rats)—hyperplastic goiter produced also
- 3 Methyl cyanide (rabbits)

F SUMMARY OF THEORIES ON EXOPHTHALMOS

- 1 Retro ocular fat increased^{8 40 4 51 5}
- 2 Edematous infiltration of^{19 9 51 6 50}
 - a Fat
 - b Orbital contents
- 3 Dilatation of capillaries^{14 44 90}
- 4 Distention of retro ocular veins
- 5 Contracture of smooth muscles³⁰
 - a Muller
 - b Hesser
 - c Landstrom
- 6 Backward pull of ocular muscles is decreased
- 7 Cellular infiltration and enlargement of extra-ocular muscles^{1 3 55}
- 8 Normal restraint of eyeballs is decreased because of wide-open lids and lid retraction

- 9 Sympathetic nervous system is hyperactive
- 10 Thyrotropic hormone
 - a Overproduction
 - b Inhibition decreased
- 11 Hypothalamic origin¹³

X SYMPTOMATOLOGY

- A GENERAL (see 26 VII)
 - 1 None referable to clinical hyperthyroidism *per se*
 - 2 Eyes
 - a Prominence
 - (1) Progressive
 - (2) Sudden
 - b Blurring vision
 - c Diplopia
 - d Photophobia
 - e Epiphora
 - f Ophthalmoplegia
 - g Pains and/or aching
 - h Tension
 - i Pressure
 - j Lack of parallelism
 - k Smarting

XI DIAGNOSIS

- A EXOPHTHALMOS
 - 1 Variable degrees
 - 2 Filter
 - a Bilateral
 - b Unilateral
- B THYROID—Normal size usually, enlarged rarely
- C LABORATORY DATA
 - 1 Iodine (protein bound)—normal
 - 2 TSH (urinary)—positive
 - 3 Basal metabolic rate
 - a Normal
 - b Decreased
 - c Increased slightly

XII DIFFERENTIAL DIAGNOSIS

- A HYPERTHYROIDISM
 - 1 Eyes may how less
 - a Edema
 - b Irritative phenomena
 - 2 Thyroid gland—enlarged
 - 3 Iodine (protein bound)—increased
 - 4 Thyrotropic hormone (TSH) (urinary)—negative
 - 5 Basal metabolic rate—elevated
 - 6 Radioactive iodine is

- a Taken up very readily by thyroid gland¹
- b Excreted in smaller quantities
- B FICTITIOUS HYPERTHYROIDISM
 - 1 History may be obtained of self medication
 - 2 Lid retraction rarely exophthalmos
 - 3 Basal metabolic rate—increased
- C NEUROCIRCULATORY ASTHENIA—see 26 VIIA
- D SCHULLER CHRISTIAN'S SYNDROME
 - 1 Diabetes insipidus
 - 2 Bone defects
 - a Skull deformities
 - (1) Geographical map
 - (2) Bone rarefaction
 - (3) Both tables involved
 - b Cysts in
 - (1) Long bones
 - (2) Pelvis
 - c Fractures
 - (1) Spontaneous
 - (2) Compressed
 - 3 Exophthalmos may be quite marked
 - 4 Xanthoma dissemination (Each of the first 3 findings are combined with No 4 or all 3 occur with it)
- E ALL FORMS OF EXOPHTHALMOS—The following group should be considered and usually may be identified by cone roentgenographic study of the orbits
 - 1 Tumors or inflammation of bony wall of orbit
 - 2 Diseases of nasal accessory or vascular sinuses
 - a Arteriovenous aneurysms
 - b Thrombophlebitis of cavernous sinus
 - 3 Intracranial tumor
 - 4 Malignant hypertension (uncommon)
 - 5 Acromegaly (rare)
 - 6 Cushing's syndrome (occasionally)

XIII COMPLICATIONS SEQUELAE AND ASSOCIATED DISEASES

- A COMPLICATIONS AND SEQUELAE
 - 1 Blindness
 - 2 Corneal ulceration
 - 3 Extension of lens
 - 4 Panophthalmia
 - 5 Ophthalmoplegia
 - 6 Optic edema
 - 7 Necrosis (?)

- 8 Entire eye or eyes protrude beyond lids

B ASSOCIATED DISEASES

- 1 Myxedema
- 2 Hypertension
- 3 Neurocirculatory asthenia it may be difficult to exclude hyperthyroidism

XIV TREATMENT

A MEDICAL

- 1 Desiccated thyroid in large doses may be tried, but temporary or slight improvement at best¹
- 2 Lugol's solution—not effective except when slight degree of hyperthyroidism may exist
- 3 Lugol's solution and desiccated thyroid^{23 47}
 - a Lugol's solution in doses of 10 to 30 minims daily (rational questionable)
 - b Desiccated thyroid is given simultaneously in sufficient dosage without producing excessive hyperthyroidism
 - c Diuretic action of thyroid is not opposed by iodine
- 4 Radioactive iodine
 - a Experimental use only at present
 - b Further increase in severe exophthalmos is not observed⁶
 - c No indication unless it effects pituitary TSH secretion
- 5 Thiouracil^{1 20 43}
 - a Indication—to replace iodine
 - b Dosage—as in hyperthyroidism
 - c Results—variable but generally poor
- 6 Stilbestrol¹ or testosterone
 - a Indication—to inhibit pituitary
 - b Results—questionable

II ROENTGEN

- 1 Pituitary or orbit may be treated^{1 21 35 43 45}
- 2 Dosage over pituitary
 - a Initially—200 r for 5 to 7 days
 - b Later—repeat in 2 or 3 months if there is no improvement
- 3 Results usually disappointing

C LOCAL²

- 1 Prevention of
 - a Scratching of scleras
 - b Infection

2 Medications for infection

- a Penicillin
 - (1) Ointment 500 to 800 units/Gm
 - (2) Saline solution 500 to 1,000 units/cc
 - (3) Allergy in 12 per cent
- b Chloromycetin
 - (1) One half per cent solution
 - (2) Preferred therapy
- c Sulfonamides
 - (1) Sulfadiazine 5 per cent ointment
 - (2) Sulfathiazole 5 per cent ointment
 - (3) Sulfanilamide 0.8 per cent in Ringer's solution

d Cortisone—see 107 VIII M 4

- 3 Anesthetic solutions are contraindicated if corneal epithelium is denuded because the following would occur
 - a Delay in healing
 - b Scarring

D SURGERY FOR MALIGNANT EXOPHTHALMOS

- 1 Operative procedure on eyes (Naffziger's method)^{31 43}
 - a Optimal time for operation is before the occurrence of
 - (1) Severe chemosis
 - (2) Corneal ulceration
 - b Technic
 - (1) Eyelids are sutured immediately before decompression
 - (2) A coronal incision is made the skin flap is reflected to the supra orbital ridges
 - (3) Two small triangular osteoplastic flaps are turned down
 - (4) Dura is then separated from the orbital plate to the sphenoid ridge
 - (5) A small portion of the lateral wall of the frontal bone adjacent to the orbital plate is removed away to allow for easier exposure
 - (6) A burr opening is made over the lateral margin of the roof of the orbit

- (7) All available bone is taken out
 - (a) The lateral wall of the orbit well down into the temporal fossa
 - (b) The posterior and inferior wall beyond the sphenoid ridge into the middle fossa to the superior orbital fissure
 - (c) Remaining orbital wall is taken away superiorly
 - (d) Optic foramina are uncapped, while medially and superiorly the bony removal is carried to the ethmoid and the frontal sinuses
 - (8) The periorbital fascia is incised in a stellate pattern, allowing the edematous orbital tissues to be decompressed
 - (9) Hemostasis is secured by ballooning out the dura with subdural saline solution
 - (10) Sulfur powder is used liberally
 - (11) Small tissue drains are left superficially
 - (12) Bone flaps are tied with black silk
 - (13) Scalp tissues sutured through out with interrupted black silk
 - (14) Bilateral operation may be performed
- c Postoperative management
- (1) Dressings are done daily with the usual precautions taken in any routine craniotomy
 - (a) These are removed gradually to avoid pain
 - (b) Patients are sensitive to light
 - (c) White ointment is applied
 - (d) Area is covered with a strip of gutta serena or boric acid which is doubled over the sponges to keep moisture in eyes
 - (e) Warm solutions are ordered after first week
 - (f) Small flaxseed poultices are used to
 - [1] Absorb moisture
 - [2] Exert pressure from their own weight (substituted for sponges)
 - (2) Drains are removed second day
 - (3) Scalp sutures are taken out the third day
 - (4) Lid sutures are taken out in 6 to 7 days
 - (5) Puffiness of lids is last to recede
 - (6) All bandages are removed from 7 to 10 days postoperatively
 - (7) Pressure is continued nightly for 2 to 3 weeks, depending on degree of conjunctival reaction
- d Results^{1 14 41 46}
- (1) Eyes may show immediate and marked recession
 - (2) Ocular movements may
 - (a) Return to normal
 - (b) Remain the same
 - (c) Become worse
 - (3) Diplopia may
 - (a) Disappear
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 - [2] Minor operative therapy
 - (4) Improvement in
 - (a) Vision
 - (b) Visual fields
 - (c) Corneal ulcers
- e Complications
- (1) Wound infections
 - (2) Cerebrospinal rhinorrhea
 - (3) Meningitis
 - (4) Frontal lobe symptoms (temporary)
 - (a) Confusion
 - (b) Delirium
 - (c) Semiconsciousness
 - (d) Disorientation
- f Outcome (35 cases at Lahey Clinic)
- (1) Satisfactory—31 (see Fig 214)
 - (2) Unfavorable—4
- 2 Radical external ethmoidectomy has given satisfactory results⁴⁸
 - 3 Subtotal thyroidectomy is not recommended because exophthalmos may increase^{15 18 77 8 47 56}
 - 4 Bilateral cervical sympathectomy—results are poor
 - 5 Hypophysectomy (partial)—may be effective, but is not recommended

XV PROGNOSIS

A TYPES

- 1 Limited or benign—*favorable*
- 2 Unlimited or malignant
 - a Rapid progress
 - b Blindness from postoperative
 - (1) Papilledema

(2) Optic atrophy

(3) Corneal ulceration

XVI CAUSES OF DEATH

A INTRACRANIAL EXTENSION OF INFECTION FROM EYES

II NATURAL

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 - (a) The lateral wall of the orbit well down into the temporal fossa
 - (b) The posterior and inferior wall beyond the sphenoid ridge into the middle fossa to the superior orbital fissure
 - (c) Remaining orbital wall is taken away superiorly
 - (d) Optic foramina are uncapped, while medially and superiorly the bony removal is carried to the ethmoid and the frontal sinuses
 - (8) The periorbital fascia is incised in a stellate pattern, allowing the edematous orbital tissues to be decompressed
 - (9) Hemostasis is secured by ballooning out the dura with subdural saline solution
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- (1) Dressings are done daily with the usual precautions taken in any routine craniotomy
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 - (b) Patients are sensitive to light
 - (c) White ointment is applied
 - (d) Area is covered with a strip of gutta percha or boric acid which is doubled over the sponges to keep moisture in eyes
 - (e) Warm solutions are ordered after first week
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- (1) Wound infections
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- f Outcome (35 cases at Lahey Clinic)
- (1) Satisfactory—31 (see Fig 214)
 - (2) Unfavorable—4
- 2 Radical external ethmoidectomy has given satisfactory results⁴⁵
 - 3 Subtotal thyroidectomy is not recommended because exophthalmos may increase^{15 18 7 3 47 56}
 - 4 Bilateral cervical sympathectomy—results are poor
 - 5 Hypophysectomy (partial)—may be effective but is not recommended



FIG. 213 EXOPHTHALMIC SYNDROME WITHOUT HYPERTHYROIDISM

Chief complaints Gradual onset nine months before admission bulging eyes and double vision which occurred in the morning at night and on looking to the extreme left. Good appetite. No weight loss.

Left

Physical examination Age 30 Weight 102 lbs Exophthalmometer readings 23-26 mm Exophthalmos on left greater than on right Thyroid normal

except for small adenoma of isthmus Pulse 84 BP 110/80

Laboratory data B.M.P. plus 1% and minus 1%.

Right

Treatment Desiccated thyroid 7 to 4 gr. daily and 5 drops of Lugol's solution for 30 months when weight was 103 lbs Pulse 96 Double vision

gone Exophthalmometer measurements gradually changed to $\frac{21-23}{115}$ mm

Patient tolerated treatment very well

Comment This is a comparatively mild degree of exophthalmos. Treatment in this case was fairly satisfactory especially in regard to the double vision.

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SECTION 34

FACTITIOUS HYPERTHYROIDISM

SYNONYMS Self induced Alimentary, Thyrototoxicosis factitia

I DEFINITION	Hyperthyroidism induced by surreptitious or known continuous administration of desiccated thyroid or thyroxin
II APPEARANCE	Typical features found in hyperthyroidism
III AGE	Adults
IV SEX	Females usually
V PHYSICAL STATUS	
A GENERAL	Hyperthyroidism findings (see 26 VI)
B EYES	Stare exophthalmos mild degrees
C THYROID	Normal or slightly enlarged
D HEART	Normal auricular fibrillation ¹ flutter, congestive failure possible (see Figs 215 and 216)
VI LABORATORY DATA	
A URINE	Iodine increased (see Charts 76 and 77) ^{8, 10}
B BLOOD CHEMICAL ANALYSES	
1 Cholesterol (plasma)	Decreased ⁶
7 Iodine	Increased ^{7, 8, 10}
C BASAL METABOLIC RATE	Increased to various degrees up to 100 per cent (see Tables 38 and 39)

TABLE 38 BASAL METABOLIC RATE AND PLASMA CHOLESTEROL ON STOPPING INGESTION OF DESICCATED THYROID⁵

BMR	PLASMA CHOLESTEROL
+ 90%	112 mg %
+ 49 "	175 mg %
+ 10%	271 mg %

II RESPONSE TO INGESTION

- 1 Detectable clinical signs and symptoms may result from as little as 2 gr a day but from 80 to 100 gr per day were taken by one patient without untoward effects
- 2 Basal metabolic rate should rise from 30 to 50 per cent with from 8 to 12 gr taken per day

VII ETIOLOGY

- A REASONS FOR OVERDOSAGE**
- 1 Therapeutic reasons
 - 2 Error in prescription
 - 3 Unfamiliarity with dosage
 - 4 Surreptitious self administration for
 - a Relief of fatigue
 - b Weight reduction
 - c Deception

VIII PATHOLOGY

- A COMMENT**—No characteristic changes in thyroid of 2 cases studied (Dr Shields Warren)

IX PATHOLOGIC PHYSIOLOGY

- A THYROID GLAND**—Thyroid inhibition (either directly or through the pituitary) occurs with a subnormal metabolic rate following discontinuance of medication⁴

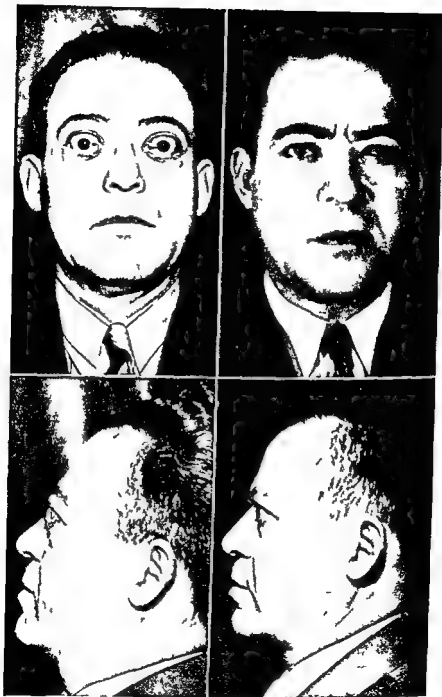


FIG 214 EXOPHTHALMOS Progressive exophthalmos after subtotal thyroidectomy for hyperthyroidism (Left top and bottom) Preoperative (Right top and bottom) After Naftziger's operation for decompression of orbits (Poppen J L Exophthalmos diagnosis and treatment of intractable cases *Am J Surg* 64 64 79)

XIII TREATMENT

- A GENERAL—Desiccated thyroid discontinued
- II SURGICAL—Subtotal thyroidectomy may be necessary as hyperthyroidism may persist due to hypersecretory diffuse hyperplastic goiter initiated by desiccated thyroid^{7 10}

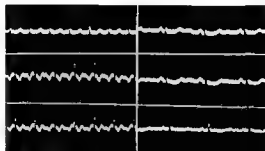
XIV PROGNOSIS

- A MAJORITY—Normal state without complications
- II MINORITY
- 1 Same course as in primary hyperthyroidism
 - 2 Persistence of hyperthyroidism
 - 3 Temporary myxedema (1 case)⁵

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FIG 215 FACTITIOUS HYPERTHYROIDISM (See also Fig 216) (Left) Auricular flutter in a patient with self induced hyperthyroidism After stopping thyroid flutter persisted (Right) Upon digitalization pulse became irregular (auricular fibrillation) and then reverted to normal rhythm (Hurxthal L M Experiences with the use of desiccated thyroid New York State J Med 44 2217 2223)



B CHOLESTEROL

- 1 Lowering of plasma cholesterol is proportional to elevation of basal metabolic rate
- 2 In myxedema, the drop in plasma cholesterol is far greater for a similar rise in basal metabolic rate (see Table 39)

C IODINE METABOLISM

- 1 Urinary excretion of iodine is
 - Increased greatly
 - b Related to intake, approximately 50 micrograms in 24 hrs for each grain of desiccated thyroid
- 2 Organic or protein bound iodine is closely correlated to the rise in basal metabolic rate¹¹
- 3 Total blood iodine has a greater variation than protein bound depending on period of time after last dose, may reach 30 to 40 gamma per cent
- 4 Radioactive¹²
 - a Uptake decreased
 - b Urinary excretion increased

TABLE 39 RELATIONSHIP BETWEEN CHOLESTEROL AND BASAL METABOLIC RATE ON ADMINISTRATION OF DESICCATED THYROID

CASE (ONE EACH)	DESICCATED THYROID	BMR	PLASMA CHOLESTEROL
Factitious hyper thyroidism	With	+ 90%	117 mg %
	Without	+ 10%	180 mg %
Myxedema	Without	- 30%	380 mg %
	With	- 5%	180 mg %

D WITHDRAWAL EFFECTS⁴

- 1 Basal metabolic rate falls
 - a Below normal, suggesting its inhibiting action on thyrotropic hormone, with gradual return to normal⁸
 - b Similar to that after
 - (1) Subtotal thyroidectomy
 - (2) Iodinization
 - c More rapidly than following
 - (1) Antithyroid drugs
 - (2) Cessation of desiccated thyroid in cases of myxedema
- 2 Cholesterol rises above the normal level in some cases and is not evidence of previous thyroid deficiency
- 3 Persistence of hyperthyroidism on

stopping medication in some cases, indicates that desiccated thyroid produced hypersecretory diffuse hyperplastic goiter⁷

E OTHER CHANGES—Similar to noninduced hyperthyroidism probably (see 26 \I)**X SYMPTOMATOLOGY****A HYPERTHYROIDISM**—Same complaints, see 26 \II**B HISTORY**

- 1 Ingestion of desiccated thyroid may or may not be admitted
- 2 Same as hyperthyroidism—see 14 \III
A 1 c

XI DIAGNOSIS**A SUMMARY**

- 1 Confession of surreptitious self administration of desiccated thyroid may not be obtained
 - a Various methods may have to be employed for detection
 - b Hospitalization (7 to 10 days) to watch patient carefully
- 2 Thyroid gland may be normal in size in spite of evident hyperthyroidism¹⁰
- 3 Laboratory data
 - a Iodine (urinary) excretion is often greater than that found in severe primary hyperthyroidism
 - b Cholesterol (plasma)
 - (1) Not diagnostic
 - (2) Proportionate to basal metabolic rate
 - c Basal metabolic rate falls rapidly after withdrawal of drug

XII COMPLICATIONS SEQUELAE AND ASSOCIATED DISEASES

- A GRAVES'S DISEASE** (see Figs 217 and 218)
 - 1 Hypersecretory diffuse hyperplastic goiter⁷
 - 2 Elevated basal metabolic rate persists after discontinuing thyroid

B EXOPHTHALMOS**C CONGESTIVE HEART FAILURE****D ACUTE PSYCHOSIS¹³****E AMENORRHEA**

XIII TREATMENT

- A GENERAL—Desiccated thyroid discontinued
- B SURGICAL—Subtotal thyroidectomy may be necessary as hyperthyroidism may persist due to hypersecretory diffuse hyperplastic goiter initiated by desiccated thyroid^{7, 10}

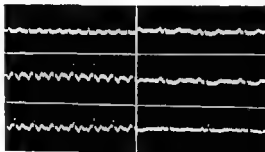
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- 6 — Experiences with use of desiccated thyroid methods of detecting self induced hyperthyroidism with report of case in which auricular fibrillation occurred, *New York State J Med* 44 2217 2223 (Oct) 1944
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FIG 215 FACTITIOUS HYPERTHYROIDISM (See also Fig 216) (Left) Auricular flutter in a patient with self induced hyperthyroidism After stopping thyroid flutter persisted (Right) Upon digitalization pulse became irregular (auricular fibrillation) and then reverted to normal rhythm (Hurxthal L M Experiences with the use of desiccated thyroid, *New York State J Med* 44 2217 2223)



II CHOLESTEROL

- 1 Lowering of plasma cholesterol is proportional to elevation of basal metabolic rate
- 2 In myxedema, the drop in plasma cholesterol is far greater for a similar rise in basal metabolic rate (see Table 39)

C IODINE METABOLISM

- 1 Urinary excretion of iodine is
 - a Increased greatly
 - b Related to intake, approximately 50 micrograms in 24 hrs for each grain of desiccated thyroid
- 2 Organic or protein bound iodine is closely correlated to the rise in basal metabolic rate¹¹
- 3 Total blood iodine has a greater variation than protein bound depending on period of time after last dose, may reach 30 to 40 gamma per cent
- 4 Radioactive¹²
 - a Uptake decreased
 - b Urinary excretion increased

TABLE 39 RELATIONSHIP BETWEEN CHOLESTEROL AND BASAL METABOLIC RATE ON ADMINISTRATION OF DESICCATED THYROID

CASE (ONE EACH)	DESICCATED THYROID	BMR	PLASMA CHOLESTEROL
Factitious hyper thyroidism	With	+ 90%	112 mg %
	Without	+ 10%	180 mg %
Myxedema	Without	- 30%	380 mg %
	With	- 5%	180 mg %

D WITHDRAWAL EFFECTS⁴

- 1 Basal metabolic rate falls
 - a Below normal suggesting its inhibiting action on thyrotropic hormone with gradual return to normal⁸
 - b Similar to that after
 - (1) Subtotal thyroidectomy
 - (2) Iodination
 - More rapidly than following
 - (1) Antithyroid drugs
 - (2) Cessation of desiccated thyroid in cases of myxedema
- 2 Cholesterol rises above the normal level in some cases and is not evidence of previous thyroid deficiency
- 3 Persistence of hyperthyroidism on

stopping medication in some cases, indicates that desiccated thyroid produced hypersecretory diffuse hyperplastic goiter⁷

E OTHER CHANGES—Similar to noninduced hyperthyroidism probably (see 26 VI)**X SYMPTOMATOLOGY****A HYPERTHYROIDISM**—Same complaints see 26 VII**B HISTORY**

- 1 Ingestion of desiccated thyroid may or may not be admitted
- 2 Same as hyperthyroidism—see 14 VIII A 1 c

XI DIAGNOSIS**A SUMMARY**

- 1 Confession of surreptitious self administration of desiccated thyroid may not be obtained
 - a Various methods may have to be employed for detection
 - b Hospitalization (7 to 10 days) to watch patient carefully
- 2 Thyroid gland may be normal in size in spite of evident hyperthyroidism¹⁰
- 3 Laboratory data
 - a Iodine (urinary) excretion is often greater than that found in severe primary hyperthyroidism
 - b Cholesterol (plasma)
 - (1) Not diagnostic
 - (2) Proportionate to basal metabolic rate
 - Basal metabolic rate falls rapidly after withdrawal of drug

XII COMPLICATIONS SEQUELAE AND ASSOCIATED DISEASES**A GRAVES'S DISEASE** (see Figs 217 and 218)

- 1 Hypersecretory diffuse hyperplastic goiter⁷
- 2 Elevated basal metabolic rate persists after discontinuing thyroid

B EXOPHTHALMOS**C CONGESTIVE HEART FAILURE****D ACUTE PSYCHOSIS¹³****E AMENORRHEA**

XIII TREATMENT

- A GENERAL—Desiccated thyroid discontinued
- B SURGICAL—Subtotal thyroidectomy may be necessary as hyperthyroidism may persist due to hypersecretory diffuse hyperplastic goiter initiated by desiccated thyroid^{7 10}

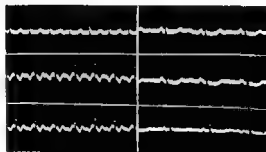
XIV PROGNOSIS

- A MAJORITY—Normal state without complications
- B MINORITY
- 1 Same course as in primary hyperthyroidism
 - 2 Persistence of hyperthyroidism
 - 3 Temporary myxedema (1 case)

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FIG 215 FACTITIOUS HYPERTHYROIDISM (See also Fig 216) (Left) Auricular flutter in a patient with self induced hyperthyroidism. After stopping thyroid flutter persisted (Right) Upon digitalization pulse became irregular (auricular fibrillation) and then reverted to normal rhythm (Hurxthal L M Experiences with the use of desiccated thyroid *New York State J Med* 44 2217 2223)



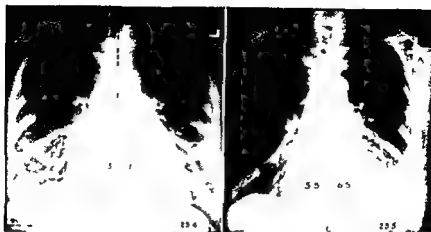


FIG 216 FACTITIOUS HYPERTHYROIDISM (See also Fig 215) Effect of factitious hyperthyroidism on the heart Female age 53 who took 15 to 20 gr or more of desiccated thyroid daily Note enlarged heart shadow on left probably due to auricular flutter The picture on right is after cessation of self induced hyperthyroidism and return of normal rhythm (Hurxthal L M Experiences with the use of desiccated thyroid New York State J Med 442 2217 2223)

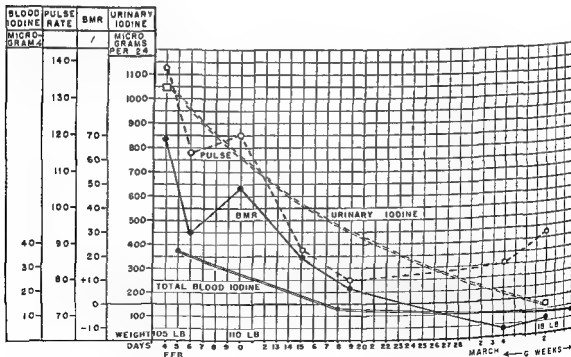


CHART 16 FACTITIOUS HYPERTHYROIDISM Observations on a patient who secretly took desiccated thyroid Note urinary output of iodine (1 050 micrograms/24 hrs) just before omission of thyroid This quantity in 24 hrs is more than is excreted by a patient with severe hyperthyroidism and much less than a hyperthyroid patient on 10 to 30 drops of Lugol's solution daily (35 000 to 90 000 micrograms) Thus urinary iodine excretion is of diagnostic value It should particularly be suspected when no enlargement of thyroid is found in a person who shows obvious clinical evidence of hyperthyroidism (Ierkin H J McFarland M D and Hurxthal L M Temporarily induced thyrotoxicosis from secretly ingested thyroid its detection by blood and urinary iodine estimations preliminary report Labey Clin Bull 2 186 188)



FIG 217 GRAVES'S DISEASE INDUCED BY TAKING DESICCATED THYROID Age 40 Mild exophthalmos following use of desiccated thyroid for obesity There was a slight enlargement of the thyroid gland and symptoms of hyperthyroidism which persisted 1 month after discontinuing thyroid Findings then Weight 164 lbs Pulse 88 Plasma cholesterol 1.6 mg % BMR plus 15% After 1 month on Lugol's solution weight 100 lbs Pulse 84 Plasma cholesterol 225 mg % BMR plus 2% One year later no iodine Weight 180 lbs Pulse 72 BMR minus 10% Exophthalmos persisted

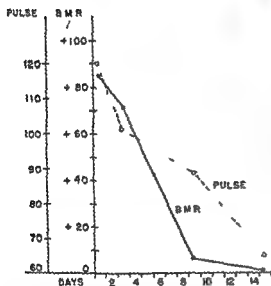


CHART 77 FACTITIOUS HYPERTHYROIDISM BMR and pulse rate in a person hospitalized for taking desiccated thyroid Note rapid fall The time taken for the BMR to return to normal after stopping desiccated thyroid is approximately the same following subtotal thyroidectomy or after iodine administration* (where a return to normal follows its use) However the drop is more precipitous in this case (Hurxthal L M Experiences with the use of desiccated thyroid New York State J Med 44 2217 2223)

* Means J H The Thyroid and Its Diseases Philadelphia Lippincott p 337



FIG 218 HYPOMETABOLISM PROBABLY THYROID DEFICIENCY AND DEVELOPMENT OF EXOPHTHALMOS ON DESICCATED THYROID

Chief complaints Swelling of face stiffness of joints and fatigue

History of present illness Nine months after a normal delivery patient gained 12 lbs Periods unchanged Developed sensitivity to cold Dry skin Somewhat forgetful and mentally slow

Left

Physical examination Age 28 Weight 149 lbs Pulse 56 BP 108/80 Some bloating of the face Dry skin Condition suggested a mild myxedema

Laboratory data Urine negative RBC 52 million Differential normal Total protein 7.9 Gm % Albumin 3.9 Gm % Globulin 3.5 Gm % Plasma cholesterol 174 mg % BMR minus 29%

Röntgenographic findings Skull normal

Treatment One gr desiccated thyroid (U S P) daily

Center

Progress

MONTHS

1½ Weight 149½ lbs Pulse 60 BMR plus 4% Marked improvement in all symptoms

8 Taking 1 gr of thyroid daily Weight 142 lbs Pulse 72 Total protein 6.1 Gm % Plasma cholesterol 120 mg % BMR plus 13% Patient noted left eye bulging Exophthalmometer reading right 16 mm left 19 mm Thyroid not palpably enlarged Thyroid medication discontinued

12 Weight 141 lbs Pulse 70 BMR plus 13% Exophthalmometer reading right 19 mm left 21 mm Noted palpitation warmth lacrimation Urinary iodine 995 micrograms/24 hrs Lugol's solution started

Right

MONTHS Weight 139 lbs BMR plus 14 12 and 8% (done elsewhere)

13 Exophthalmometer reading right 20 mm left 22 mm Propylthiouracil 300 mg a day

14 Weight 139½ lbs Pulse 72 BMR plus 1% Plasma cholesterol 133 mg % Exophthalmometer reading right 18 mm left 20 mm

30 Weight 135 lbs Pulse 100 Exophthalmometer reading right 21 mm left 22 mm Thyroid not enlarged Three months pregnant No treatment in past 16 months Feels fairly well

Comment At no time could a hyperplastic enlarged gland be felt The excretion of urinary iodine taken 16 days after discontinuing Lugol's solution was excessive and suggestive of factitious hyperthyroidism although this could not be proved The normal plasma cholesterol is not consistent but quite possible with myxedema The increase in total protein is characteristic

SECTION 35

TUMORS OF THE THYROID

I DEFINITION

A neoplasm within the thyroid gland which may be benign or malignant, single or multiple discrete invasive or metastasizing usually associated with euthyroidism, but occasionally with hyperthyroidism or hypothyroidism

II APPEARANCE

Not abnormal, 'goiter' or lumps in neck of various sizes rarely hyper or hypothyroid characteristics

III AGE

Any, average around 45 years^{20 22 23 6 31 47}

IV SEX

Approximately 85 per cent females^{11 23 47}

V PHYSICAL STATUS

A GENERAL

Euthyroidism usually, dysthyroidism rarely, about 5 per cent associated with hyperthyroidism,² or very rarely hypothyroidism

B LARYNX (voice)

Normal or recurrent laryngeal paralysis, displacement of thyroid cartilage

C NECK

1 Thyroid

Localized discrete firm mass may be palpated in gland or multiple hard lumps beyond it, may be fixed to surrounding tissues (see Figs 219 220 and 224)

2 Lymph glands

Normal or enlarged, especially above isthmus (Delphian gland¹) if malignant tumor

VI LABORATORY DATA

A GENERAL (urine, hematology and blood chemical analyses)

Normal

B IODINE

Variable

C BASAL METABOLIC RATE

Normal

VII ROENTGENOGRAPHIC FINDINGS

A TRACHEA

Normal or may reveal displacement or compression

B CHEST

Normal, intrathoracic extension or metastatic lesions

C BONES

Normal or metastatic areas predominantly osteolytic⁴²

VIII ETIOLOGY

A UNKNOWN

B FETAL ANLAGE—Occurrence

1 Nodular goiters—12 per cent

2 Hyperplastic glands—8 per cent

C PAPILLARY CYSTADENOMA—Origin and extension uncertain

1 Thyroid to cervical lymph glands⁷

2 Aberrant thyroid tissue to thyroid gland (see Fig 232)⁴⁸

D COLLOID NODULES (see 17 VII)

TABLE 40 KNOWN PRESENCE OF THYROID TUMOR PRIOR TO DIAGNOSIS²³

GROUP	HISTOLOGIC TYPE	YEARS (AVERAGE) OF EXISTENCE OF TUMOR BEFORE DIAGNOSIS
I	Fetal adenoma with invagination	108
	Papillary adenocystoma	4.5
II	Papillary adenocarcinoma	4.1
	Alveolar adenocarcinoma	8.2
III	Small-cell carcinoma	5.1
	Giant cell carcinoma	15.3

IX PATHOLOGY^{3 29 33 51}

A BENIGN TUMORS

1 Characteristics

- a Encapsulated mass
- b Clinically ranges from 2 to 10 cm in diameter
- Weight on removal between 25 and 200 Gm

2 Specific types

a Embryonal adenoma

- (1) Resembles embryonic thyroid tissue
- (2) Cells are
 - (a) Moderate in size
 - (b) Polyhedral in shape
 - (c) Packed closely
 - (d) Arranged in
 - [1] Solid masses
 - [2] Strands
 - [3] Small clusters
 - (e) Embedded in fairly edematous fibrous tissue stroma
- (3) Vascular supply
 - (a) Very abundant
 - (b) Thin walled vessels favor occurrence of
 - [1] Hemorrhages
 - [2] Cystic degeneration
- (4) Extensive hemorrhage may cause a sharp increase in the size of the nodule
- (5) Later there may be
 - (a) Fibrosis
 - (b) Calcification

b Alveolar (fetal) adenoma (see Fig 221)

- (1) Origin sometimes from fetal cell rests in intra acinar parenchyma
- (2) Formation of small acini with very little colloid
 - (a) Clusters devoid of lumina (rare)
 - (b) Cell masses widely spaced
 - (c) Epithelium cuboidal
- (3) Stroma edematous
- (4) Changes which may take place
 - (a) Hemorrhage
 - (b) Cystic degeneration
 - (c) Fibrosis
 - (d) Calcification
- (5) Blood vessels abundant

c Simple adenoma

- (1) Thyroid tissue fairly well differentiated
- (2) Epithelium with little evidence of functional activity
- (3) Hyperfunctioning solitary adenoma
 - (a) Epithelium high columnar
 - (b) Colloid present
 - (c) Remainder of thyroid normal
- (4) Hurthle cell adenoma (very rare type)^{3 50}
 - (a) Acini
 - [1] Small
 - [2] Colloid
 - [a] Scant
 - [b] Absent
 - (b) Cells
 - [1] Large
 - [2] Acidophilic
 - [3] Cytoplasm clear
 - [4] Nuclei slightly larger than normal

d Colloid adenoma

- (1) Follicles
 - (a) Huge
 - (b) Distended with colloid
 - (c) Papillary projections absent
 - (d) Scalloping of colloid not found
- (2) Epithelium
 - (a) Flat
 - (b) Low cuboidal
- (3) Stroma moderate amounts
- (4) Spontaneous hemorrhage frequent with sudden enlargement

e Papillary adenocystoma

- (1) Encapsulated mass
- (2) Papillae lined with tall columnar epithelium
- (3) Fluid within cyst may be
 - (a) Brownish
 - (b) Hemorrhagic
 - (c) Filled with small flecks of cholesterol
- (4) Follicles
 - (a) Well formed occasionally
 - (b) Scattered
 - (c) Scant in colloid
- (5) More apt to become malignant than other adenomas (see below)

B MALIGNANT TUMORS

- 1 Adenomas with invasion (benign metastasizing—Group I)
 - a Histologic criteria for inclusion under malignancy are the invasion of
 - (1) Capsule
 - (2) Blood vessels
 - (3) Lymphatic channels
 - (4) Surrounding or distant tissues
 - b Types
 - (1) Alveolar adenoma (see Fig 222)
 - (2) Papillary adenocystoma (see Fig 223)
- 2 Adenocarcinoma (Group II)
 - a Origin
 - (1) Thyroid gland which has been normal
 - (2) Various adenomas frequently
 - b Characteristics
 - (1) Hard
 - (2) Asymmetrical
 - (3) Gradual increase in size of thyroid
 - (4) Fixed to surrounding structures
 - (5) Metastases to lymph nodes may be found
 - c Microscopic
 - (1) Cellular anaplasia
 - (2) Mitotic figures
 - (3) Tumor giant cells are present
 - (4) Capsule absent

- (5) Invasion of
 - (a) Surrounding structures
 - (b) Blood vessels
 - (c) Lymph glands
- d Types
 - (1) Papillary (see Figs 224 227)
 - (a) More anaplasia than alveolar
 - (b) Solid clusters of tumor cells
 - (2) Alveolar (see Fig 228)
 - (a) Acinar formation may be marked
 - (b) Follicles have little colloid
 - (c) Normal thyroid architecture with only slight maintenance of alveolar form may be seen
- 3 Carcinoma simplex (Group III)
 - a Small cell carcinoma (see Fig 229)
 - (1) Types
 - (a) Compact—may or may not originate from pre existing adenoma
 - (b) Diffuse—practically never arises from former adenoma
 - (2) Characteristics are the same as for other malignant growths
 - (3) Microscopic
 - (a) Compact
 - [1] Cells

TABLE 41 TYPES OF THYROID MALIGNANCY (1928 1947 Inclusive)

GROUP	HISTOLOGIC TYPE	INDIVIDUAL NUMBER	TOTAL NUMBER	PER CENT
I	Adenoma with invasion of		108	24.6
	Blood vessel	12		
	Capsule and lymphatics	61		
II	Capsule or lymphatic and blood vessels	35	203	46.2
	Adenocarcinomas			
	Papillary	154		
III	Alveolar	49	108	24.6
	Carcinoma simplex			
	Small cell	72		
IV	Giant cell	36	20	4.6
	Mucellaneous			
	Hurthle cell	7		
	Fibrosarcoma	7		
	Lymphoma	3		
	Epidermoid	2		
	Unclassified	1		
	Grand total		439	

- [a] Small
- [b] Packed closely
- [2] Alveolar formation absent
- [3] Nuclei
 - [a] Prominent
 - [b] Hyperchromatic
 - [c] Filled with numerous mitotic figures
- [4] Invasion of
 - [a] Blood vessels
 - [b] Lymphatics
- (b) Diffuse type (diagnostic problem, for some feel it should be grouped with the lymphomas rather than the epithelial type)
 - [1] Cells
 - [a] Polyhedral
 - [b] Cytoplasm scant
 - [c] Pseudoalveolar groupings
 - [2] Mitotic figures vary
 - [3] Intimate relationship of stroma and tumor cells is most striking feature
- b Giant cell carcinoma (see Figs 230 and 231)
 - (1) Clinical course rapid
 - (2) From pre existing adenoma
 - (3) Characteristics
 - (a) Large
 - (b) Fleshy
 - (c) Very vascular type
 - (d) Fixation
 - (e) Infiltration
- (4) Microscopic
 - (a) Giant cells
 - [1] Numerous
 - [2] Variable
 - (b) Very vascular
 - (c) Necrosis
- 4 Miscellaneous types
 - a Epidermoid carcinoma (squamous cell)
 - (1) Origin from
 - (a) Thyroglossal duct
 - (b) Metaplasia of thyroid epithelium
 - (2) Description ~~as~~ for the other malignant tumors
 - (3) Microscopic
 - (a) Epithelial cells
 - [1] Numerous
 - [2] Clusters (pearl formation)
 - [3] Strands
 - (b) Keratinization in variable degrees
 - b Fibrosarcoma (rare)
 - (1) Gross appearance
 - (a) Gray pink
 - (b) Fleshy
 - (2) Microscopic—spindle cells arranged in strands
 - c Lymphoma
 - (1) Secondary to lymphomatous process elsewhere
 - (2) Pathologic changes as other lymphoid tumors
 - d Hurthle cell—same as adenoma, but with malignant features
 - e Unclassified

TABLE 42 THYROID CANCER—AGE AND SEX DISTRIBUTION
(1928 to 1935 Inclusive*)

GROUP	HISTOLOGIC TYPE	PATIENTS			AGE (YEARS)	
		Females	Males	Total	Average	Range
I	Fetal adenoma with invasion	43	6	49	45.2	20-72
	Papillary adenocystoma	41	7	48	46.2	9-0
II	Papillary adenocarcinoma	33	5	38	44.8	13-80
	Alveolar adenocarcinoma	19	5	24	44.1	9-70
III	Small cell carcinoma	26	4	30	46.5	9-72
	Giant cell carcinoma	8	1	9	59.4	36-70
		170	28	198		

* See Table 45 for outcome

X SYMPTOMATOLOGY

A BENIGN TUMORS

- 1 None except when large enough to produce pressure
- 2 Hemorrhage may occur with acute pressure symptoms

B MALIGNANT TUMORS

- 1 None sometimes for years
- 2 The following may develop
 - a Hoarseness
 - b Dysphagia
 - c Dyspnea
 - d Stridor
 - e Edema of face
 - f Venous congestion of neck veins
 - g Metastatic lesions causing
 - (1) Bone pain
 - (2) Fractures

C THYROID FUNCTION

- 1 Euthyroidism usual
- 2 Hypothyroidism occasionally
- 3 Hyperthyroidism rare

TABLE 43 INCIDENCE OF MALIGNANCY IN SOLITARY OR MULTIPLE NODULAR OR OTHER GOITERS

TYPE OF GOITER	PER CENT MALIGNANT
Clinically presumed solitary nodules ^{10 11 29}	10.8-24.5
Suspected nonfunctioning nodule by radioactive iodine technic (Dobyns) ^{1 13}	18
Surgically verified solitary nodules (estimated) ^{10 29 34}	18
Multiple nodules ^{4 21 4 43}	0.5-1.1
Hyperplastic goiter ^{11 25 47}	<1
All goiters (surgical) ^{4 11 3 43 47}	2.5-3
Incidence in relation to malignancy of other organs ^{8 9 30}	1-3

XI DIAGNOSIS

A HISTORY

- 1 Unreliable, unless rapid growth
- 2 Duration of neoplasm is not important (see Table 40)
- 3 Recent onset of symptoms is suggestive

B CHARACTERISTICS

- 1 Localized, discrete, firm tumor
- 2 Fixation to surrounding structures
- 3 Multiple, hard lumps beyond thyroid gland
- 4 Cervical lymph gland involvement
- 5 Delphian gland enlargement believed to be helpful¹
- 6 Recurrent laryngeal paralysis
- 7 Less radioactive emanation from nodule than surrounding tissue¹
- 8 Exclusion of other lesions (see below)
- 9 Roentgenographic evidence of metastases
- 10 Histologic studies are essential for (except in obvious and hopeless malignancy)
 - a Diagnosis
 - b Proper therapy

XII DIFFERENTIAL DIAGNOSIS³

A THYROIDITIS—see 19 XI 21 XI 22 XI

B LATERAL APERRANT THYROID TUMOR

1 Description

- a Outline discrete sometimes bilateral
- b Consistency
 - (1) Firm
 - (2) Soft
- c Size—variable usually small gland like structures
- d Locations
 - (1) In front of sternomastoid muscle
 - (2) Close to internal jugular vein

TABLE 44 DISTRIBUTION OF KNOWN METASTASES²³

	NECK	LUNGS	MEDIASTINUM	BONE	SOFT TISSUES	VISCERAL
Papillary adenocystoma	7	2		1		1
Papillary adenocarcinoma	2	2	1			1
Alveolar adenocarcinoma	4	3	1			1
Small-cell carcinoma	6	5		2	2	
Giant-cell carcinoma	2	2	2	1		
Total	21	14	4	4	2	3

- (3) Deep in neck as carotid body tumor
 - (4) Behind thyroid
 - Other facts
 - (1) Unilateral
 - (2) Superficial
 - (3) Movable
 - (4) Mass may exist for years as enlarged lymph gland or glands
 - 2 Incidence
 - a Approximately 0.2 per cent of goiter cases
 - b Majority are malignant⁴⁵
 - 3 Origin
 - a Ultimobranchial bodies — present trend opposes this view
 - b Extension of
 - (1) Papillary cystadenoma of thyroid³¹
 - (2) Other thyroid malignancies, especially papillary carcinoma³¹
 - 4 Pathology—usually papilliferous type
 - 5 Treatment—surgical removal to determine malignancy and hemithyroidectomy (see 35 XIV C)
- C THYROGLOSSAL CYST OR FISTULA⁸**
- 1 Description (see Figs 233 and 234)
 - a Outline
 - (1) Oval
 - (2) Round
 - b Consistency
 - (1) Elastic
 - (2) Fluctuating
 - c Size is
 - (1) Variable
 - (2) Increased gradually
 - d Locations
 - (1) In front of thyrohyoid membrane
 - (2) Midline or to left of midline
 - Other data
 - (1) Superficial
 - (2) Immobile but moves with swallowing
 - (3) Firmly attached to hyoid bone
 - (4) Inflammation may develop suddenly
 - (5) Rupture is possible
 - (6) Any age group susceptible
 - 2 Incidence
 - a About 1 in 50 of surgical diseases of the thyroid
 - b One in approximately 500 goiter patients
- 3 Etiology**
- a Failure of the thyroglossal duct to disappear
 - b Fistula
 - (1) Passes usually from foramen cecum down to the thyroid isthmus
 - (2) Is attached to hyoid bone in many cases
 - (3) May be result of
 - (a) Ruptured cyst
 - (b) Incision
- 4 Pathology**
- a Wall of cyst may be thick
 - b Epithelium
 - (1) Cylindrical
 - (2) Ciliated
 - c Cyst contents
 - (1) Cholesterol
 - (2) Viscid material
 - (3) Purulent if inflammation is present
 - d Osteomyelitis of hyoid bone may develop (rare)
- 5 Symptomatology**
- a None, except for cosmetic complaint
 - b Onset at puberty
 - c Localized pain if inflamed
- 6 Treatment—every part of entire tract or cyst must be excised completely or else condition may recur**
- a Section of hyoid bone should be removed
 - b Tract is followed to base of tongue
- D BRANCHIAL CYST AND SINUS**
- 1 Description**
- a Outline
 - (1) Round
 - (2) Smooth
 - (3) Unilocular
 - b Consistency
 - (1) Fluctuant
 - (2) Soft
 - c Size—about hen's egg or smaller
 - d Location—swelling behind or below angle of the jaw
 - e Other facts
 - (1) Superficial
 - (2) Bulge outward as they enlarge
 - (3) Abscess may form
 - (4) Rupture occasionally

- (5) Grow slowly
- (6) Movable, but only moderately
- (7) History of recurrent swelling and soreness sometimes with internal discharge (see branchial sinus below)
- 2 Incidence
 - a About 1 in 200 cases of surgical disease of the thyroid
 - b Sex—males more often affected
- 3 Etiology
 - a Second branchial cleft, rarely the first, fails to become obliterated with the formation of the cyst
 - b Branchial sinus
 - (1) Empties into pharynx close to tonsil
 - (2) Descends beneath diaphragm muscle
- 4 Pathology
 - a Epithelial lining
 - (1) Squamous stratified
 - (2) Columnar
 - (3) Ciliated
 - b Wall contains lymphoid tissue
 - c Cyst contents
 - (1) Fluid
 - (a) Colorless
 - (b) Thin
 - (c) Viscid
 - (d) Opaque
 - (2) Fatty debris
 - (3) Cholesterol
 - (4) Epithelial cells
 - d Epithelium may develop (unusual)
- 5 Symptomatology
 - a Progressive painless swelling under angle of jaw
 - b Sinus
 - (1) Discharge escapes through a dimple in front of sternomastoid muscle
 - (2) Dimple moves with swallowing
 - (3) Exit of tract shows flecks of pigmentation on the skin
- 6 Treatment
 - a Excision of entire cyst
 - b The following should be avoided because they re-establish the fistula or fluid
 - (1) Drainage
 - (2) Curettage
 - (3) Caustics

E LARYNGOCELE (rare)

- 1 Characteristics
 - a Round mass opposite or above level of larynx
 - b Unilateral
 - c Enlargement on swallowing or holding breath
 - d Air may be demonstrated in it by fluoroscopic examination
 - 2 Symptomatology
 - a None usually
 - b Hoarseness
- ## F METASTATIC NODULES IN THYROID OR NECK GLANDS¹
- 1 Origin
 - a Stomach
 - b Lungs
 - c Lips
 - d Tonsils
 - e Pharynx
 - f Larynx
 - 2 Early—glands are
 - a Single
 - b Movable
 - c Small
 - d Hard
 - 3 Later—glands are
 - a Large
 - b Fixed
 - c Widespread

G PRIMARY CARCINOMAS

- 1 Origin
 - a Branchial remnants
 - b Parathyroids
- 2 Incidence—very rare

H LINGUAL GOITER (see Fig 235)

- 1 Description
 - a Outline
 - (1) Surface smooth
 - (2) Irregular if cysts or colloid nodules are present
 - (3) Round
 - (4) Lobulated
 - b Consistency
 - (1) Hard
 - (2) Soft
 - (3) Cystic
 - c Size—cherry to egg
 - d Locations
 - (1) Supralingual—on tongue
 - (2) Intra lingual—within substance of posterior third of tongue

- (3) Sublingual—beneath the tongue
- e Other data
 - (1) Immobile
 - (2) Very vascular mucous membrane congested over it
 - (3) Pedunculated occasionally
 - (4) Laryngoscopic examination is sometimes necessary for diagnosis
- 2 Incidence
 - a Data—approximately 1 in every 5,000 to 10,000 cases of thyroid disease
 - b Sex—females affected more often than males
- 3 Etiology—the thyroid gland fails to descend into its normal position
- 4 Pathology
 - a Colloid goiter which may develop
 - (1) Cystic degeneration
 - (2) Hemorrhage
 - b Hyperplastic goiter
 - c Malignancy
- 5 Symptomatology
 - a Onset
 - (1) At birth
 - (2) During puberty
 - (3) Insidious
 - b Fullness in throat
 - c Speech impairment
 - d Hemoptysis with ulceration of mucous membranes
 - e Thyrotoxicosis, rarely
 - f Sudden increase in size due to hemorrhage
 - g Large goiter may produce
 - (1) Cough
 - (2) Dyspnea
 - (3) Dysphagia
- 6 Treatment—removal of goiter, only if
 - a Tumor interferes with swallowing
 - b Hemorrhage occurs
- 7 Result—myxedema develops postoperatively
- I INFLAMMATORY GLANDS
 - 1 They are related to adjacent focus of infection
 - 2 Recent origin can be confirmed
- J GUMMATOUS LYMPH NODES OF SYPHILIS
 - 1 Rare
 - 2 Serologic tests are positive
- K TUBERCULOUS CERVICAL ADENITIS
 - 1 Tuberculosis may be present elsewhere
- 2 Multiple involvement of cervical glands
- 3 Early stage
 - a Firm
 - b Round
 - c Small
 - d Isolated
 - e Painless
 - f Movable
- 4 Later stage
 - a Fused
 - b Irregular
 - c Adherent
 - d Tender
 - e Overlying skin may be red
 - f Caseation may form
 - g Calcification (demonstrated by roentgenograms)
- 5 Microscopic section for definite diagnosis
- L HODGKIN'S DISEASE (including lymphosarcoma, lymphoblastoma—see Fig 236)
 - 1 Lymph glands
 - a Noninflammatory
 - b Grapelike, may become quite large
 - c Movable early, later fixed
 - d Necrosis absent
 - e Majority involved
 - 2 Pel Epstein fever in some cases
 - 3 Diagnosis by biopsy
- M LYMPHATIC LEUKEMIA
 - 1 Acute
 - a Youthful person
 - b Nodes
 - (1) Growth rapid
 - (2) Multiple involvement
 - c Tonsils enlarged
 - d Hemorrhages are subcutaneous
 - e Blood picture typical
 - 2 Chronic
 - a Lymph nodes
 - (1) Enlarged
 - (2) Indurated
 - (3) Generalized
 - b Blood picture diagnostic
 - c Debility
- N PARATHYROID ADENOMA—see 38
- O NEUROFIBROMA
 - 1 Origin anywhere in nerve tissue
 - 2 Positive diagnosis by biopsy
- P CAROTID BODY TUMOR
 - 1 Mass is located at the notch made by the division of the common carotid into its external and internal branches

- 2 It enlarges upward and inward toward the pharynx

Q DEEP CERVICAL ABSCESS

- 1 Characteristics
 - a Inflammatory exudate is found beneath the deep cervical fascia
 - b Infected areas are within the region from which they drain
 - c Stonelike
 - d Large
 - e Fixed
 - f Firm
 - g Brawny edema
 - h Superficial redness
- 2 Symptomatology
 - a Local soreness
 - b Painful swallowing
 - Difficulty breathing due to edema of larynx
 - d Fever

XIII COMPLICATIONS SEQUELAE AND ASSOCIATED DISEASES

A GENERAL

- 1 Metastases
 - a Cervical lymph nodes
 - b Lungs
 - c Bones (see Fig 237)
 - d Other areas
- 2 Hemorrhage
- 3 Tracheal compression
- 4 Laryngeal nerve may be affected
- 5 Inanition

XIV TREATMENT

- A INTRODUCTION—Surgery is indicated for all tumors (benign and malignant) after careful assessment of probable

- 1 Chance of malignancy
 - a Actual
 - b Potential
- 2 Risk
- 3 Duration of life in presence of advanced age and/or some other incurable disease

B BENIGN TUMORS—Operative procedure—

- 1 Anesthesia—cyclopropane oxygen
- 2 Curved collar incision, which is higher on side of goiter
- 3 Fat and platysma divided
- 4 Deep cervical fascia incised

- 5 Sternocleidomastoid muscle freed
- 6 Median incision of deep cervical fascia
- 7 Division of prethyroid muscles on involved side
- 8 Elevation and medial retraction of adenoma
- 9 Division of middle thyroid veins
- 10 Lateral dissection
- 11 Ligation of inferior thyroid artery in continuity
- 12 Exposure of
 - a Recurrent nerve
 - b Inferior parathyroid
- 13 Application of clamps to superior and inferior portions of lobe containing adenoma
- 14 Excision of adenoma leaving a thin shell of normal thyroid tissue
- 15 Reconstruction of remnant
- 16 Prethyroid muscles sutured
- 17 Closure of skin and platysma with clips
- 18 Drain is used only if there is a large dead space

C MALIGNANT TUMOR¹

- 1 Surgical
 - a Adenoma with blood vessel invasion only—simple excision
 - b Adenoma with capsule or lymph gland invasion
 - (1) Radical neck dissection of lymph nodes on affected side
 - (2) Hemithyroidectomy
 - (3) Roentgen therapy (postoperative)
 - c Carcinoma (Grade II) with capsule invasion—as above, including removal of
 - (1) Internal jugular vein
 - (2) Sternocleidomastoid muscle
 - d Carcinoma (Grade III)
 - (1) Extensive removal
 - (2) Detachment of carcinomatous tissue from trachea
 - (3) Tracheotomy to prevent compression during roentgen therapy
- 2 Postoperative roentgen therapy¹ ■ ■ ■
73 25 5 ■ 9 39 49
 - a Comment
 - (1) Radiation therapy is advisable immediately after recovery from the operation

- (2) Entire tumor bed must be exposed to radiation, but normal tissue should be protected because of the following changes from heavy radiation
 - (a) Telangiectasia of the skin
 - (b) Soft tissue induration
 - (c) Certain degree of fixation of the neck, if portals are large enough to produce muscle fibrosis
 - (3) Dosage must be sufficient to destroy the tumor tissue completely
 - (a) Lethal dosage has been established in certain tumors
 - (b) In alveolar adenocarcinoma, the dosage required for its destruction is so great that it is not advisable to treat a large field because of the damage to surrounding normal tissues
 - (c) The probable cause of failure in lesions other than alveolar adenocarcinoma, is the presence of metastases outside of the treated area
 - (d) Tumor may frequently return in an area after treatment with the estimated lethal dose
- b Procedure**
- (1) Cross fire method is preferable
 - (2) One treatment is given daily
 - (3) Three portals are used
 - (a) One portal on each side of the neck and the third in the midline
 - [1] Care should be taken not to overlap the fields
 - [2] Greatest percentage should enter the tumor bed
 - (b) The size of the portal depends on the
 - [1] Proportions of the original growth
 - [2] Degree of substernal extension
- c Dosage**
- (1) Total amount of 6 000 r measured in air are delivered to the skin during one series of treatment
 - (a) A total of 2 000 r is given through each portal
 - (b) Each portal is treated daily after the first three treatments, using 150 r to each (a total of 450 r daily)
 - (c) If the patient is debilitated it is necessary to decrease the dose to 100 r to each portal daily
 - (2) Total depth dosage—6 000 r given externally provides a dose of approximately 4 800 r, 2 cm beneath the skin
 - (3) The following factors are used
 - (a) K V P 200, milliamperes 20, 24 r units/min
 - (b) Filter 2 mm copper, 1 mm of aluminum added
 - (c) Distance 50 cm, portal 7 to 10 sq cm, half value layer 13
 - (4) Treatments carried out daily, except Sunday, unless complications occur
- d Complications**
- (1) Radiation sickness
 - (a) Frequent complaint when large amounts are delivered
 - (b) Symptomatology
 - [1] Nausea
 - [2] Vomiting
 - [3] Irritability
 - [4] Restlessness
 - (c) Management
 - [1] Daily dose decreased
 - [2] Cortisone orally
 - (d) This is not serious usually ceases within 72 hrs
 - (2) Dermatitis
 - (a) Development in some cases has been observed about 7 to 10 days after irradiation
 - (b) Quite severe occasionally
 - (c) Six to 8 weeks may be required to heal entirely
 - (3) Laryngitis—disappears in 9 to 10 weeks time
 - (4) Tracheitis—recovery in 9 to 10 weeks

TABLE 45 THYROID CANCER—SURVIVAL AFTER TREATMENT
TOTAL 198 PATIENTS³³

GROUP	HISTOLOGIC TYPE	TOTAL NO		5 YEARS		10 YEARS		15 YEARS		20 YEARS	
		OF	PATIENTS	NO	PER CENT	NO	PER CENT	NO	PER CENT	NO	PER CENT
I	Fetal adenoma with invasion	49	38	77.5	10	38.7	7	14.2	5	10.1	
	Papillary adenocarcinoma	45	31	64.5	23	47.9	13	28.0	2	4.1	
II	Papillary adenocarcinoma	39	30	78.9	20	52.6	7	18.4	4	10.5	
	Alveolar adenocarcinoma	24	7	29.1	5	20.8	1	4.1	0		
III	Giant cell carcinoma	9	2	22.2	1	11.1	0	0	0		
	Small cell carcinoma	30	6	20.2	2	6.6	0	0	0		

(5) Difficulty in swallowing—hospitalization may be necessary

(6) Sloughing of tissues—rare

(7) Myxedema

(8) Anemia

■ Management

(1) Reassurance

(2) Inform patient regarding possibility of

(a) Sore throat

(b) Blistering of the skin

3 Thiouracil—will readily suppress hormone production by functioning metastases from thyroid adenocarcinoma

D THYROID METASTASES (pulmonary and osseous)

1 Roentgen therapy³⁴

a Indications

(1) Pain

(2) Limited number of metastases

(3) Evidence of growth as noted by repeated observation some remain stationary for years especially in the lungs

(4) Radiosensitivity as determined by biopsy especially

(a) Papillary adenocarcinoma

(b) Small-cell carcinoma

(c) Benign metastasizing tumor

b Dosage—as for neck except when metastases in

(1) Liver

(2) Retroperitoneal region

■ Results

(1) No statistical data

(2) Favorable in Groups I and II because

(a) Condition is quite stationary

(b) Roentgen therapy is very effective

2 Radioactive iodine therapy (see 26 \\\ I H)^{15 19 20 29 31 40}

a This mode of treatment is still in its experimental stages but indications are the same as for roentgen therapy

b Isotopes are taken up infrequently by metastatic areas which can be demonstrated by

(1) Geiger Muller apparatus

(2) Radioautographic determinations³¹

c Radioactive material is linked with the structural qualities of the tumor, especially as to

(1) Follicular pattern

(2) Presence of colloidlike material

d Although over 50 per cent of metastatic lesions take up radioactive iodine as shown by radioautographs of biopsied tissue (Groups I and II), very few accumulate enough to warrant radioactive iodine therapy with out inducing greater avidity^{14 46}

e Dosage

(1) Functional metastases (rare) by radioactive iodine alone^{41 48}

(a) Single dose of I¹³¹ about 50 to 150 microcuries

(b) Cumulative dosage about 150 to 900 microcuries

(2) Nonfunctional metastases

(a) Methods to increase iodine uptake by tumor^{41 46}

[1] Total thyroidectomy

[2] Injection of thyrotropic hormone

[3] Thiouracil ingestion

- (b) Administration of radioactive iodine as above
- (c) Time and frequency of dosage individualized
- f Complications¹⁶
 - (1) Acute hyperthyroidism (within 2 weeks)
 - (2) Spinal fluid pressure may increase
 - (3) Amenorrhea
 - (4) Blood dyscrasia with a decrease in
 - (a) Red blood count
 - (b) Hemoglobin
 - (c) Lymphocytes
 - (d) Platelets
 - (5) Myxedema
- g Results⁴¹⁻⁴⁸
 - (1) Estimated 40 to 50 per cent receive considerable benefit, justifying the therapy
 - (2) Under 25 per cent are greatly improved, and life is prolonged
 - (3) Cures yet to be established

XV PROGNOSIS⁴⁹⁻⁵³

A BENIGN TUMORS

- 1 Excellent
- 2 Metastases have been known to occur from histologically benign lesions

II MALIGNANT TUMORS

- 1 Groups I and II comprise 80 per cent of total
 - a Surgery without roentgen therapy—data inconclusive
 - b Surgery followed by roentgen therapy—results favorable
- 2 Group III
 - a Surgery alone—short lived
 - b Surgery and roentgen therapy—one third that of Groups I and II
- 3 Miscellaneous types
 - a Variable
 - b Similar to Group III

XVI CAUSES OF DEATH

A METASTASES

B CACHEXIA

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FIG 219 CARCINOMA OF THYROID Age 60 Lump in throat for 12 years Loss of 20 lbs in 6 months Cough



FIG 220 CANCER OF THYROID Inoperable Compare with Figure 236 showing similar growth due to lymphosarcoma



FIG 221 FETAL ADENOMA Irregular colloid deposits follicles and fetal cell masses separated Struma edematous and vascular Little scarring Low power (x 28)



FIG 222 (Top left) ALVEOLAR ADENOMA with blood vessel and lymphatic invasion. Verhoeff's elastic tissue stain accentuates elastica of blood vessels ($\times 72$) (Meissner W A and Lahey F H. Carcinoma of the thyroid in a thyroid clinic J Clin Endocrinol 8:49, '61)

FIG 223 (Top right) PAPILLARY ADENOCYSTOMA showing local invasion of capsule ($\times 72$) (Meissner W A and Lahey F H. Carcinoma of thyroid in a thyroid clinic J Clin Endocrinol 8:749, '61)



FIG 224 PAPILLARY ADENOCARCINOMA OF THYROID (See also Fig 225) Age 34. Götter noted 6 years increasing in size. BMR minus 20%. Pathologist suggested origin of tumor in an adenoma. Operation followed by irradiation with recovery.



FIG 219 CARCINOMA OF THYROID Age 60 Lump in throat for 12 years Loss of 20 lbs in 6 months Cough



FIG 220 CANCER OF THYROID Inoperable Compare with Figure 236 showing similar growth due to lymphosarcoma

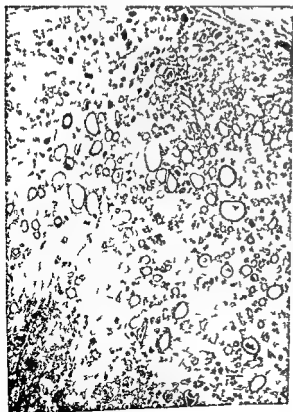


FIG 221 FETAL ADENOMA Irregular colloid deposits follicles and fetal cell masses separated Struma edematous and vascular Little scarring Low power ($\times 28$)



FIG 228 ALVEOLAR ADENOCARCINOMA (x 28) (Meissner W A and Lahey F H Carcinoma of the thyroid in a thyroid clinic J Clin Endocrinol 8 749 '61)



FIG 229 SMALL CELL COMPACT CARCINOMA SIMPLEX. (x 141) (Meissner W A and Lahey F H Carcinoma of the thyroid in a thyroid clinic J Clin Endocrinol 8 749 '61)



FIG 225 PAPILLARY ADENOCARCINOMA OF THYROID REMOVED FROM PATIENT SHOWN IN FIGURE 224

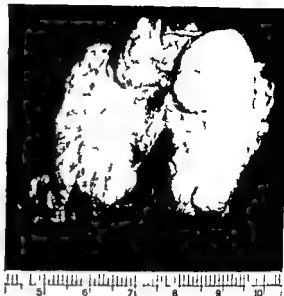


FIG 227 CARCINOMA THYROID CROSS SECTION OF GROSS SPECIMEN Age 63 Six months duration Hard nodule to left of isthmus Question whether mass was carcinoma or localized thyroiditis Pathologic report papillary adenocarcinoma Treatment 10 x 200 r after surgery Patient ■ turned 11 years later with an adenoma in right lobe which was removed Pathologic report adenoma In good health 3 years later (Lahey F H Hare H F and Warren S Carcinoma of the thyroid Ann Surg 112 977 1005)



FIG 226 PAPILLARY ADENOCARCINOMA MITOSIS (x 29) (Meissner W A and Lahey F H Carcinoma of the thyroid in a thyroid clinic J Clin Endocrinol 8 749 761)



FIG 233 THYROGLOSSAL CYST AND DUCT Excised thyroglossal cyst and duct. A section of the hyoid bone is included as well as muscles up to the floor of the mouth. This was necessary in order to remove the tract completely and give a permanent cure.



FIG 234 THYROGLOSSAL CYSTS Thyroglossal cysts in young, middle and elderly persons. Note midline position and tendency to enlarge. The cysts are usually located above the thyroid cartilage and very rarely below it. (Top left) Sinus (spontaneously formed) from thyroglossal cyst with faint outline of latter above it. (Top right) Small thyroglossal cyst with sinus opening just below it. (Bottom left) Medium sized thyroglossal cyst without a sinus. (Bottom right) Large thyroglossal cyst in elderly man (Clute H. M. and Smith L. W. Carcinoma of the thyroid gland. Arch. Surg. 18:120).



FIG 230 GIANT CELL CARCINOMA OF THYROID Age 64 Swelling in neck noted for 1 year Similar swelling stated to have been present at 18 and subsequently disappeared Roentgenogram revealed intrathoracic goiter which was partially calcified Symptoms hoarseness some dyspnea and pain in chest Weight loss 20 lbs Venous pressure 280 mm of water Larynx displaced to right and no action of left vocal cord seen Preoperative diagnosis adenomatous goiter possibly malignant At operation tumor was not adherent (confined to left lobe) removed in mass Pictures taken with infra red photographs showing dilated veins Second photograph (right) 15 days after operation (See Fig 231 for microscopic) Roentgen therapy following operation No recurrence 4 years later

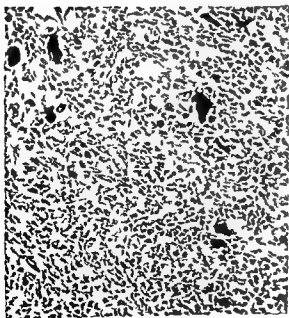


FIG 231 GIANT CELL CARCINOMA SIMPLEX ($\times 142$) (See also Fig 230) (Meissner W A and Labev F H Carcinoma of the thyroid in a thyroid clinic J Clin Endocrinol 8 749 761)



FIG 232 LYMPH GLAND CONTAINING METASTATIC PAPILLARY ADENOCARCINOMA FREQUENTLY CALLED MALIGNANT ABERRANT THYROID (Warren S and Feldman J D The nature of lateral aberrant thyroid tumors Surg Gynec & Obst 88 31-44)



FIG 233 THYROGLOSSAL CYST AND DUCT Excised thyroglossal cyst and duct. A section of the hyoid bone is included as well as muscles up to the floor of the mouth. This was necessary in order to remove the tract completely and give a permanent cure.

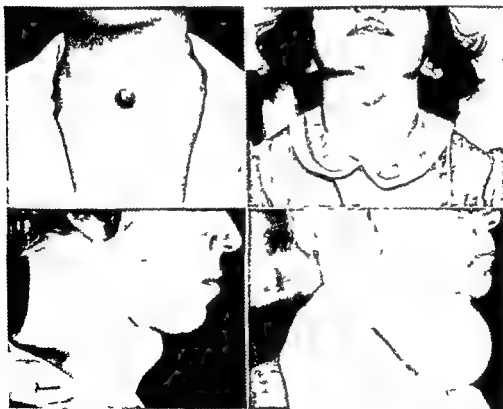


FIG 234 THYROGLOSSAL CYSTS Thyroglossal cysts in young, middle and elderly persons. Note midline position and tendency to enlarge. The cysts are usually located above the thyroid cartilage and very rarely below it. (Top left) Sinus (spontaneously formed) from thyroglossal cyst with faint outline of latter above it. (Top right) Small thyroglossal cyst with sinus opening just below it. (Bottom left) Medium sized thyroglossal cyst without a sinus. (Bottom right) Large thyroglossal cyst in elderly man. (Clute H. M. and Smith L. W. Carcinoma of the thyroid gland. Arch. Surg. 18:120)



FIG 230 GIANT CELL CARCINOMA OF THYROID Age 64 Swelling in neck noted for 1 year Similar swelling stated to have been present at 18 and subsequently disappeared Roentgenogram revealed intrathoracic goiter which was partially calcified Symptoms hoarseness some dyspnea and pain in chest Weight loss 20 lbs Venous pressure 280 mm of water Larynx displaced to right and no action of left vocal cord seen Preoperative diagnosis adenomatous goiter possibly malignant At operation tumor was not adherent (confined to left lobe) removed in mass Pictures taken with intra red photography showing dilated veins Second photograph (right) 15 days after operation (See Fig 231 for microscopic) Roentgen therapy following operation No recurrence 4 years later

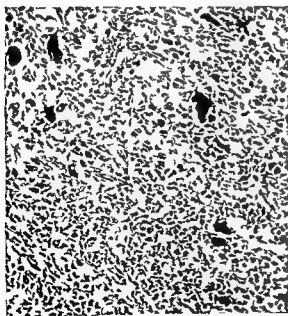


FIG 231 GIANT CELL CARCINOMA SIMPLEX (x 142) (See also fig 230) (Meissner W A and Lahey F H Carcinoma of the thyroid in a thyroid clinic J Clin Endocrinol 8 749 761)



FIG 232 LYMPH GLAND CONTAINING METASTATIC PAPILLARY ADENOCARCINOMA FREQUENTLY CALLED MALIGNANT ABERRANT THYROID (Warren S and Feldman J D The nature of lateral aberrant thyroid tumors Surg Gynec & Obst 88 31 44)

CHAPTER 4

Parathyroids

PRECLINICAL

Section 36 PRELIMINARY

- I HISTORY
- II ANATOMY
- III EMBRYOLOGY
- IV CONGENITAL ANOMALIES
- V HISTOLOGY
- VI FUNCTIONS
- VII CHEMISTRY
- VIII BIO ASSAY
- IX PATHOLOGY
- X CLASSIFICATIONS
- XI CHIEF CLINICAL FINDINGS OF HYPOSECRETION
- XII CHIEF CLINICAL FINDINGS OF HYPERSECRETION
- XIII EXAMINATION OF PATIENT

CLINICAL

Section 37 PRIMARY HYPOPARATHYROIDISM

38 PRIMARY HYPERPARATHYROIDISM

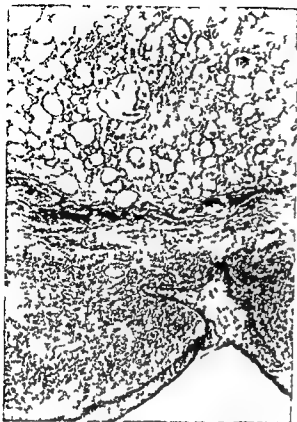


FIG 235 LINGUAL THYROID TISSUE
Removed from base of tongue Myxedema
usually follows

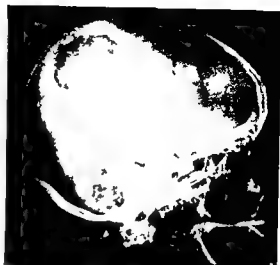


FIG 236 THYROID PAPILLARY ADENOCARCINOMA METASTATIC LESION IN SKULL
This type of lesion has been reported to
yield to radioactive iodine therapy after
total thyroidectomy



FIG 236 LYMPHOSARCOMA (Left) Tumor of neck suggesting malignancy of thyroid. Biopsy showed lymphosarcoma Roentgen therapy reduced size markedly (Right) Effect was only temporary

SECTION 36

PRELIMINARY

I HISTORY

- | | | |
|------|--------------------------------------|---|
| 1709 | Courtial ¹⁰ | Bone changes characteristic of osteitis fibrosa cystica noted |
| 1815 | Clarke ¹¹ | Tetany described for first time |
| 1830 | Steinheim ⁴ | Parathyroid tetany differentiated |
| 1839 | Stanski ³ | Osseous lesions reported due to hyperfunctioning parathyroid glands |
| 1850 | Corvisart ¹ | The term 'tetany' was coined |
| 1855 | Remak ¹⁰ | First demonstration of the parathyroids |
| 1862 | Trousseau ¹⁰ | A sign of tetany (Trousseau's sign) discovered |
| 1864 | Engel ¹⁸ | Case of generalized fibrocystic osteitis recorded (later pointed out by von Recklinghausen) |
| 1864 | Virchow ²⁸ | Parathyroid glands described |
| 1873 | Erb ¹⁰ | Increased irritability of motor nerve in tetany proved by electrical stimulation (Erb's sign) |
| 1876 | Chvostek ¹⁰ | A sign of tetany observed (Chvostek's sign) |
| 1880 | Sandstrom ¹⁰ | Lower set of glands found and named parathyroids |
| 1880 | Weiss ³² | Tetany recognized in humans following thyroidectomy |
| 1891 | Gley ³³ | Parathyroids are independent of thyroid gland |
| 1891 | von Recklinghausen ³⁰ | Osteitis fibrosa cystica reported |
| 1891 | Neumann ⁴¹ | Method for determining phosphorus |
| 1892 | von Eiselsberg ⁹ | Transplantation of parathyroids in thyroidectomized cats |
| 1893 | Chantemesse and Marie ⁹ | Variability in number of parathyroids in man |
| 1895 | Kohn ³⁴ | Anatomic and embryologic data on parathyroids |
| 1896 | Halsted ⁴ | Cases of chronic experimental tetany recorded |
| 1896 | Vasale and Generali ³⁷ | Removal of parathyroids probably cause tetany |
| 1898 | Lusena ³⁷ | Tetany treated by parathyroid emulsion and grafts |
| 1898 | Welsh ⁴³ | Histologic description of parathyroids |
| 1899 | Kocher ³⁴ | Parathyroid tumor noted |
| 1900 | de Santi ¹⁷ | He is usually accredited with first description of a parathyroid tumor |
| 1901 | Loeb ³⁴ | Inhibitory effect of calcium on muscular contraction proved |
| 1903 | Erdheim ¹⁰ | Hyperplasia of parathyroids resulted from osteomalacia and rickets |
| 1904 | Albers Schonberg ¹ | Condition of marble bones (osteopetrosis) discovered |
| 1904 | Askanazy ² | Cystic bone disease associated with parathyroid tumors reported |
| 1905 | MacCallum ⁶⁰ | Hypertrophy of the parathyroids occurred following certain diseases |
| 1907 | Forsyth ¹ | Marked variability of parathyroids in number size shape and position emphasized |
| 1907 | Parhon and Urechie ⁴³ | Intraperitoneal calcium ameliorated tetany in animals with thyroparathyroidectomy |
| 1909 | MacCallum and Voegtlin ⁴¹ | Hypocalcemia demonstrated as the etiology of tetany on removal of parathyroids |
| 1915 | Lyman ³⁸ | Method for determining calcium in urine and feces |

II ANATOMY¹³

A LOCATION AND DESCRIPTION

- 1 Shape
 - a Oval
 - b Disk
- 2 Color
 - a Yellow
 - b Reddish brown
- 3 Groups^{3 7}
 - a Upper pair
 - (1) Lateral lobes of thyroid
 - (a) On dorsum
 - (b) Within capsule
 - (c) In lobulations
 - (2) One on either side at level of lower border of cricoid cartilage, behind junction of pharynx and esophagus
 - b Lower pair
 - (1) Dorsum of lower border of lateral thyroid lobes
 - (2) Inferior to thyroid
 - (3) Within the mediastinum
- 4 Number^{2 8 11}
 - a From 2 to 12 may be present at age 4
 - b More than 4—33 per cent
 - c. Less than 4—1 per cent¹⁰

B SIZE

- | | |
|-------------|----------|
| 1 Length | 3-15 mm |
| 2 Width | 2-6 mm |
| 3 Thickness | 0.5-4 mm |

C WEIGHT

- | | |
|---------------------------------|--------------------|
| 1 Range | 20-40 mg |
| 2 Average | 35 mg |
| 3 Total | 1 Gm ¹² |
| 4 Greater in women ⁹ | |

D BLOOD AND LYMPH SUPPLY^{4 8 11}

- 1 Arteries (closely related to that of thyroid gland)
 - a Inferior thyroids
 - b Anastomatic channel between inferior or superior thyroid vessels
- 2 Veins—same as arterial supply
- 3 Lymph vessels—probably belong to the thyroid system

E NERVES

- 1 Laryngeals
 - a Recurrent
 - b Superior
- 2 Cervical sympathetic
- 3 No secretory nerves have been demonstrated¹

III EMBRYOLOGY¹⁻⁴

A ORIGIN—Entodermal cells which sprout from dorsolateral walls of third and fourth gill clefts

B FORMATION

- 1 Superior group
 - a Primordium arises from fourth pouch adjacent to lateral thyroid body
 - b Parts migrate cephalically to a position along the dorsal aspect near superior poles of thyroid lobes
- 2 Inferior group
 - a Anlage is derived from third pouch just adjacent to the thymus
 - b Portion becomes detached and migrates caudally to be embedded in the thyroid lobes

C TIME OF DEVELOPMENT—At 7 weeks (fetus—17 mm crown rump), parathyroids are associated with thyroid

IV CONGENITAL ANOMALIES

A VARIATIONS

- 1 Number and size
 - a Two to 12 glands⁴
 - b Weight differs markedly
- 2 Blood supply

B ABERRANT TISSUE

- 1 In thyroid
- 2 Near larynx
- 3 At carotid sheath
- 4 Behind esophagus
- 5 In mediastinum
 - a Posterior
 - b Anterior
- 6 Within thymic rests
- 7 Near pericardium

C ABSENT¹V HISTOLOGY^{1-3 8 9}

A TYPES OF CELLS

- 1 Chief (principle water clear or wasser helle)
 - a Shape
 - (1) Large
 - (2) Round
 - b Cytoplasm
 - (1) Pale
 - (2) Clear
 - (3) Granules—rare
 - (4) Mitochondria
 - (5) Golgi apparatus

- 1915 Schlagenhauser⁵⁰ Parathyroid tumor caused von Recklinghausen's disease, i.e., *osteitis fibrosa cystica*
- 1917 Halverson and Bergeim⁵¹, Lyman⁵², Marriott and Howland⁵³ Procedure for analysis of blood calcium
- 1919 Huldshinsky⁵⁴ Curative effects of ultraviolet rays on rickets
- 1921 Steenbock, Sell and Buell⁵⁵ Vitamin A separated from vitamin D
- 1922 Weil⁵⁶ Precocious puberty, pigmentation and peculiar variety of osteospathyrosis in a female
- 1923 Hanson⁵⁷ Effective parathyroid extract prepared
- 1923 Salvesen^{47, 48} Toxic theory of tetany refuted and low blood calcium recognized as the cause
- 1924 Berman⁷ Potent parathyroid extract made
- 1924 Steenbock and Nelson⁵⁸, Hess⁵⁹ A ration which induced rickets in rats could be made anti rachitic by exposing it to ultraviolet light
- 1925 Collip¹² Parathyroid extract (parathormone) prepared and standardized
- 1925 Collip and Letch³⁴ First effective parathyroid extract in the treatment of tetany due to hypoparathyroidism
- 1925 Mandl⁶ Successful removal of a parathyroid tumor from a patient with bone cysts and calcinuria hyperparathyroidism thus established
- 1926 Collip¹³ Experimental hyperparathyroidism produced hypercalcemia and hypophosphatemia
- 1926 Jones³³ Cod liver oil used to prevent tetany in animals
- 1928 Gold⁸ Second case of von Recklinghausen's disease cured by surgical removal of parathyroid tumor
- 1928 Urechia and Popoviciu⁵⁶ Irradiated ergosterol given for postoperative tetany in man
- 1929 Albright and Ellsworth² Primary action of parathyroids on phosphorus metabolism postulated
- 1929 Barr, Bulger and Dixon⁶ Term 'hyperparathyroidism' suggested
- 1930 Hannon, Shorr, McClellan and DuBois³ First demonstration of hypercalcemia in a patient with osteitis fibrosa cystica (case of Captain Martell)
- 1931 Bourdillon et al.⁸ A crystalline compound 'calcaferol' isolated from irradiated ergosterol which had 400 000 times the antirachitic value of cod liver oil
- 1932 Askew et al.⁴, and Windhaus et al.¹⁰⁰ Pure crystals of vitamin D
- 1932 Hamilton and Schwartz⁷ Method for determining small amounts of parathyroid hormone
- 1932 Hamilton and Schwartz²⁰ Evidence presented for hyperfunction of parathyroid glands in children with vitamin D deficiency
- 1933 Holtz³¹ Dihydrotachysterol (A T 10) introduced for treatment of tetany
- 1937 Barney and Sulkowitch⁵ Test for excess calcium in the urine

B HORMONE

1 Introduction

- a Two sites of primary action of the parathyroid hormone have been postulated and both may be involved, depending on known and perhaps some unidentified factors⁴
1 10 1 1

(1) Kidneys

- (a) Phosphate excretion is increased through decreased tubular resorption^{1 3 10 1}
20 25

- (b) Excretion of phosphate lowers the serum phosphorus

- (c) Serum calcium rises by an unknown mechanism in response to the decreased serum phosphorus

- (d) Hypercalcemia is associated with an increased urinary excretion of calcium how ever the latter may begin before the serum calcium level is above normal

- (e) Excess urinary excretion of calcium causes withdrawal of calcium from the bones if the daily intake is insufficient to balance the loss²⁰

- (f) If the primary action is also on the bones certain environmental conditions there may be necessary to provoke this effect (see below)

- (g) In support of the belief that a low serum phosphorus produces hypercalcemia a high intake of phosphorus in hyperparathyroidism raises the serum phosphorus and lowers the serum calcium to normal

- (h) Calcium is not drawn from the bones in hyperparathyroidism when the calcium intake is adequate for the bones will recalcify and a positive calcium balance can be established

(2) Bones

- (a) Several possibilities exist in liberation of calcium from the matrix

- (b) Osteoclastic formation and activity cause dissolution of bone^{2 10 1 1}

- [1] Stimulation is directly by parathyroid hormone

- [2] Response to stress or change in

- [a] Calcium phosphorus ratio

- [b] Other environmental factors

- b The problem is not solved

- (1) Enzymes may be involved in this mechanism further studies are required¹³

- (2) The reader is referred to Albright and Reifenstein for further discussion on the pros and cons of the primary sites of action⁴

- 2 Functions as deduced from parathyroid hormone injections in normal or parathyroid deficient animals or men

a Urinary excretion¹¹

- (1) No alteration in creatine or creatinine until kidney damage occurs¹⁷

(2) Increased

- (a) Nitrogen (temporary)¹¹

- (b) Calcium¹²

- (c) Phosphate^{1 10 17}

- (d) Chlorides

- (e) Total volume

b Serum

(1) Decreased

- (a) Phosphorus (also lowered in corpuscular ester)^{1 6 8}
17 20

- (b) Chlorides

(2) Increased

- (a) Calcium²⁰

- (b) Magnesium (slight)⁴

- (c) Alkaline phosphatase if bone changes occur

(3) pH to acid side⁸

- c Fecal excretion—no consistent finding^{1 4}

- d Bones—see 36 VI D 2

- e Gastro intestinal function is to maintain normal rate of calcium absorption⁷

- f Augmentation of vitamin D effect possibly through greater intestinal absorption¹⁸

- Nucleus
 - (1) Large
 - (2) Spherical
 - d Rich in glycogen
 - e Distinct membrane
 - 2 Oxyphil (acidophil colloid)
 - a Shape
 - (1) Larger than chief cells
 - (2) Polygonal
 - b Cytoplasm
 - (1) Strongly acidophilic
 - (2) Granules
 - (a) Numerous
 - (b) Fine
 - (3) Mitochondria
 - (4) Golgi apparatus
 - c Nucleus
 - (1) Small
 - (2) Stain—deep
 - 3 Intermediate
 - a Shape—variable
 - b Cytoplasm
 - (1) Paler than chief cells
 - (2) Stain—faint acid
 - (3) Granules
 - (a) Fine
 - (b) Less than in chief cells
 - c Nucleus
 - (1) Smaller than chief cells
 - (2) Stains darker than others
- B CELLULAR CORDS (see Fig 238)**
- 1 Arrangement
 - a Continuous masses of cells
 - b Columns
 - c Acini which occasionally contain colloid with small amounts of iodine
 - 2 Between groups of cells
 - a Fatty deposits which increase with age
 - b Sinusoidal capillaries
 - c Delicate fibrous or reticular stroma investing individual cells or cell groups
- C RELATIONSHIP OF CELLS**
- 1 Chief cells are more numerous than the oxyphils
 - 2 Sequence from masses to cords to acini is regarded by some as due to aging
 - 3 Functional relationship unknown
- D DISTRIBUTION OF CELLS AT VARIOUS AGES**
- 1 Fetus—cells arranged in loose reticular manner, except at periphery where there is a single layer of closely packed cells⁴
 - 2 Postnatal
 - Chief or principal cells
 - (1) Round
 - (2) Cytoplasm scant
 - (3) Nucleus deeply stained
 - b Dark cells
 - (1) Round
 - (2) Cytoplasm
 - (a) Fine
 - (b) Granular
 - (c) Deep eosinophilic stain
 - 3 After age of seven
 - a Oxyphilic cells develop
 - (1) Large, polygonal shape
 - (2) Cytoplasm rich in eosinophilic granules
 - (3) Groups of 3 to 4, or single
 - (4) Later increase in number at periphery of gland
 - b Transition of different cellular types is seen
 - 4 Puberty
 - a Gland is of normal adult size
 - b Chief cells mostly
 - c Further increase in oxyphil cells
 - d Delicate capsule dips and divides gland into lobules
 - 5 Adult
 - a Glandular activity increased
 - b Fat deposits
 - c Colloid vesicles may be present
 - d Alveolar arrangement of cells may be found
 - Cells may be columnar
 - f Further increase in oxyphil cells
 - g Blood vessels are numerous
- VI FUNCTIONS**
- A GLAND AS A WHOLE**
- 1 Chief purpose is to secrete parathyroid hormone however, it is not absolutely necessary to life
 - 2 It maintains and renders available the proper calcium and phosphorus ratio in the blood and the tissues, to which the skeleton can adapt its architecture to varying conditions (see 103 \ \ III for calcium phosphorus and bone metabolism)
 - 3 Relationship or dependence upon the pituitary gland has not been demonstrated conclusively

- 4 Urinary
 - a Output decreased
 - b Calcium increased¹
 - c Phosphorus increased¹
- 5 Blood
 - a Decrease in
 - (1) Chlorides (whole blood)
 - (2) Volume
 - b Increase in
 - (1) Red cells (hemoconcentration)
 - (2) Hemoglobin
 - (3) Nonprotein nitrogen (blood)
 - (4) Calcium (serum) (eventually falls)^{3 5}
 - (5) Phosphorus (serum)
 - (6) Viscosity
- 6 Fecal excretion—increased
 - a Calcium
 - b Phosphorus
- 7 Death
- 8 Other endocrine glands not affected significantly

E HISTOPHYSIOLOGY¹

- 1 Observations are fragmentary
- 2 Origin of secretion
 - a Chief cells are probably source of hormone
 - b Large water clear cells in abnormal conditions undoubtedly secrete hormone
 - c Oxyphil cells may be secretory
- 3 Oxyphilic cells increase with age and accumulate acidophilic protein, the significance of which is unknown
- 4 Inclusion bodies are found in some animals but not in man
- 5 Glycogen demonstrable in parenchyma (man)
- 6 Alkaline phosphatase is
 - a Present in endothelial walls of sinusoids (rats)
 - b Decreased slightly after hypophysectomy

F ACTIVITY AT DIFFERENT PERIODS IN LIFE

- 1 Parathyroids of the fetus may function during intra uterine life^{1 3}
- 2 Histologic variations from birth to senility suggest quantitative differences in elaboration of the hormone but actually very little is known

VII CHEMISTRY

A COMPOSITION OF HORMONE

- 1 Proteinlike substance which has never been isolated in pure form^{1 3 5}
- 2 Amorphous powder
- 3 Dried preparation contains
 - a Nitrogen 15.5 per cent
 - b Iron (traces)
 - c Sulfur (traces)

B PROPERTIES⁴

- 1 Destroy by boiling in
 - a Hydrochloric acid 10 per cent
 - b Sodium hydroxide, 5 per cent
 - c Pepsin at 37° C
 - d Tyrosine at 37° C
 - e Proteolytic enzymes
- 2 Soluble in
 - a Water
 - b Alcohol 80 per cent
- 3 Insoluble in
 - a Ether
 - b Acetone
 - c Pyridine

C PREPARATION¹

- 1 Extract is obtained by boiling fresh bovine parathyroid glands with aqueous hydrochloric acid
- 2 The hormone is precipitated with trinitrophenol
- 3 Precipitate is then extracted by acid acetone and alcohol and the hormone is reprecipitated with excess acetone
- 4 Final product is dissolved in water

VIII BIO ASSAY¹

A METHODS

- 1 Normal dogs (cats or rabbits)
 - a Unknown extract is injected subcutaneously into 10 animals (10-15 kg.) and the rise in serum calcium is determined
 - b Test is not very satisfactory because of many variable factors
 - c One USP unit equals 1/100 of the amount of extract which increases the serum calcium 1 mg % within 16 to 18 hrs following a subcutaneous injection in normal dogs
 - d Parathyroid extract (USP) standardized of that 1 cc exerts specific activity of 80 to 120 units

C PARATHYROIDECTOMY (see 36 \I)⁵ 11 15-18

- 1 Neuromusculature
 - a Irritability
 - b Tetanic manifestations
 - Psychic aberrations
 - d Cerebral calcification
 - e Intracranial pressure, if increased sufficiently, may be followed by optic edema
 - f Hyperpyrexia³
- 2 Bones
 - a Skeletal density increased
 - b Osteoclastic activity decreased
 - Abnormally soft (animals)
 - d Callous formation is delayed (animals)
 - e Osseous growth is not usually disturbed
- 3 Gastro intestinal
 - a Anorexia (animals, man)
 - b Aversion to phosphates
 - c Craving for calcium salts
 - d Diarrhea (animals man)
 - e Interference with intestinal absorption of vitamins in the usual dietary quantities is probable¹³
 - f Calcium absorption is decreased and an ordinary intake of calcium is insufficient to control tetany
 - (1) Addition of from 5 to 10 times the usual intake of calcium will cause
 - (a) Calcium (serum) elevation
 - (b) Phosphorus (serum) reduction
 - (c) Increased excretion of urinary calcium
 - (2) Effectiveness of above is probably greater if some parathyroid function remains
- 4 Ectoderm⁶ 7
 - a Teeth
 - (1) Dentine defects⁸ 11
 - (2) Atrophy of odontoblasts (animals)
 - (3) Brittle⁹
 - b Loss of hair
 - c Nails
 - (1) Deformed
 - (2) Hypoplastic
- 5 Cataracts are common⁷
- 6 Urine
 - Calcium—decreased (no calcium is

excreted below the serum level of 7 to 8 mg %; rare exceptions¹)

- b Phosphorus—decreased⁹ 10

7 Blood

- a Hemoconcentration
- b Sugar—normal
- Protein (serum)—increased due to hemoconcentration
- d Calcium (serum)—decreased
- e Phosphorus (serum)—increased

8 Fecal calcium excretion increased

■ Pregnancy and offspring

- a Fertility decreased
- b Fetus is smaller than normal
- c Gestation is prolonged¹
[The above (a to c) are controlled in animals by a high calcium and/or low phosphorus intake]

- d Calcium cannot be mobilized from the bones (rats)

10 Herbivora (high calcium intake) are less sensitive than carnivora (high phosphorus intake)¹

D HYPERHORMONAL EFFECTS (see 38)¹ 11

- 1 Parathyroid glands—cytologic alterations of hyperfunction²

2 Bones

- Osteoclastic activity is increased eventually creating a loss of calcium with

- (1) Resorption fibrosis
- (2) Dense bone formation
- (3) Picture of *ostitis fibrosa cystica*³⁻¹⁰ 1-14

- b Small and continued doses in animals may provoke only osteoblastic activity resulting in hard, sclerotic bone¹⁻⁴

- c Calcification hypertrophy of epiphyseal cartilage develops in growing mice

3 Bodily changes

- a Calcification of viscera⁵ 7

- b Reduction in gastric

- (1) Contents

- (2) Acidity

- Hemorrhage into

- (1) Gastro intestinal tract

- (2) Bone marrow

- d Growth is retarded (immature rats)

- e Scleroderma-like condition¹⁵

- f Dehydration

- 4 Urinary
 - a Output decreased
 - b Calcium increased¹
 - c Phosphorus increased¹
- 5 Blood
 - a Decrease in
 - (1) Chlorides (whole blood)
 - (2) Volume
 - b Increase in
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 - d Parathyroid extract (U.S.P.) standardized of that 1 cc exerts specific activity of 80 to 120 units

- 2 Normal rats—determination of
 - a Increased urinary calcium
 - b Bone changes

IX PATHOLOGY

A GROSS¹

- 1 Atrophy^{1 9}
- 2 Cysts
- 3 Adenomas (benign) or parathyroidoma (see 38 \ A 1 a)^{4 6 14 16 19}
 - These outnumber simple hyperplasia in hyperparathyroidism
- b Multiple tumor formation is difficult to distinguish from hyperplasia
- 4 Primary hyperplasia or hypertrophy (see 38 \ A 1 b)^{7 4 7 10}
- 5 Secondary hyperplasia causes enlargement, up to 30 times normal, of all the parathyroid glands¹
- 6 Carcinoma (see 38 \ A 1 c)^{1 14 17 18}

B MICROSCOPIC

- 1 Normal (see 36 IV)³
- 2 Atrophy (see 37 \ B 1 c)
- 3 Cysts (see 37 \ B 1 d)
- 4 Adenoma (see 38 \ II 1 a)
- 5 Primary hyperplasia (see 38 \ B 1 b)
- 6 Secondary hyperplasia (see 38 \ II 1 c)
- 7 Carcinoma (see 38 \ B 1 d)
- 8 Rare¹
 - a Inflammation
 - (1) Acute or chronic
 - (2) Miliary tuberculosis
 - (3) Syphilis
 - b Fibrosis—possibly as a result of inflammation but significance is questionable
 - c Passive congestion
 - d Infarction
 - e Hemorrhage
 - f Edema
 - g Colloid degeneration
 - h Fatty infiltration
 - i Amyloidosis
 - j Hydropic changes
 - k Metastatic involvement

C HISTOPHYSIOLOGY

- 1 Hypoparathyroidism
 - a In idiopathic type—no data on changes in remaining cells of parathyroids
 - b Bone—no histologic data
 - c Teeth—failure of dentine calcification^{9 10}

- d Eyes—deposition of calcium phosphate causing cataracts
- Calcification in brain—no data
- f Calcium deposits however, do not occur in same tissues as in hyperparathyroidism¹¹

2 Hyperparathyroidism

- Parathyroid gland
 - (1) No proven relationship between
 - (a) Types of cells
 - (b) Clinical picture
 - (2) Changes which suggest an excess secretion are absent, except for an increased number of cells
 - (3) Follicles and colloid are seen more frequently in hyperparathyroid adenomas
- b Bones¹²
 - (1) Osteoclasts and osteoblasts increase over the normal number with bone involvement
 - (2) When excessive parathyroid activity ceases, osteoclasts disappear while the osteoblasts remain as well as cover areas occupied by the former
 - (3) Deposition of calcium in osteoid areas takes place slowly
 - (4) Cysts with fibrous tissue may also recalcify after osteoid tissue has been laid down
- c Calcium deposits are found in many tissues, if blood level is very high¹¹
 - (1) Conjunctivae
 - (2) Corneae
 - (3) Lungs
 - (4) Stomach
 - (5) Kidney tubules
 - (6) Muscles

3 Other conditions which alter cells

- a Hypoplasia
 - (1) Parathyroid tumor of one or more glands causes hypoplasia of the others
 - (2) Moniliasis
 - (3) Constant use of parathyroid hormone
- b Hyperplasia of chief cells principally may be preceded by
 - (1) Avitaminosis D
 - (2) Renal failure
 - (3) Malignant metastases to bone
 - (4) Acromegaly

X CLASSIFICATIONS**A COMPREHENSIVE LIST OF POSSIBLE FACTORS—see 2 VIII A****E HORMONAL**

- 1 Pseudohypoparathyroidism or euparathyroidism with an absence of target organ response
- 2 Hypoparathyroidism or deficiency of parathyroid hormone
- 3 Hyperparathyroidism or excess of parathyroid hormone
 - a Primary
 - b Secondary

C CLINICAL

- 1 Parathyroid tumors with euparathyroidism
- 2 Pseudohypoparathyroidism
- 3 Hypoparathyroidism
 - a No tetany
 - b Latent tetany
 - c Manifest tetany
- 4 Hyperparathyroidism
 - a Primary
 - (1) Chronic
 - (a) Chemical changes only
 - [1] Hypercalciuria
 - [2] Hypercalcemia
 - [3] Hypophosphatemia
 - (b) Renal involvement
 - (c) Bone disease
 - [1] Osteitis fibrosa cystica
 - [2] Osteitis fibrosa generalisata
 - (d) Bone and renal disease
 - (2) Acute—with any of the above conditions
 - b Secondary
 - (1) Avitaminosis D or resistance to it
 - (a) Rickets (children)
 - (b) Osteomalacia (adults)
 - (2) Steatorrhea
 - (3) Other causes of calcium deprivation
 - (a) Inadequate calcium intake
 - (b) Pregnancy [with b (1)]
 - (c) Lactation [with b (1)]
 - (4) Renal disease
 - (a) Tubular insufficiency and renal acidosis—Milkman's syndrome
 - (b) Glomerular insufficiency

with renal osteitis fibrosa cystica

[1] Nephritis

[2] Congenital malformation of genito urinary tract

(c) Hyperamino aciduria—Fanconi's syndrome

XI CHIEF CLINICAL FINDINGS OF HYPOSECRETION**A SUMMARY (see 37)**

- 1 Mental changes
 - a Retardation
 - b Delirium
 - c Anxiety
 - d Depression with sense of impending disaster
- 2 Cerebral calcification
- 3 Neuromuscular
 - a Hyperexcitability effects may be
 - (1) Mild
 - (2) Severe as in tetany
 - b Numbness and tingling of extremities
 - c Stiffness of facial muscles especially about lips
 - d Spasm
 - (1) Eyelids
 - (2) Laryngeal
 - (3) Carpal pedal
 - (4) Anal
 - e Abdominal rigidity
 - f Strabismus
 - g Convulsions
- 4 Ectodermal defects of
 - a Hair
 - b Teeth
 - c Nails
- 5 Cataracts
- 6 Serum
 - a Calcium—below 9 mg %
 - b Phosphorus—above 4 mg %
- 7 Bone density increased

XII CHIEF CLINICAL FINDINGS OF HYPERSECRETION**A SUMMARY (see 38)**

- 1 General
 - a Vague complaints of ill health
 - (1) Anorexia
 - (2) Weight loss
 - (3) Weakness
 - (4) Polydipsia

- b Arteriosclerosis
- 2 Genito urinary system
 - a Polyuria
 - b Renal
 - (1) Colic
 - (2) Stones
 - (3) Sand
 - (4) Failure (uremia)
- 3 Musculature
 - a Myalgia
 - b Atony
- 4 Serum
 - a Calcium range—11 to 18 mg %
 - b Phosphorus—below 4 mg %
- 5 Bones
 - a Pathologic fractures
 - b Shrinkage of height
 - (1) Scoliosis
 - (2) Kyphosis
 - (3) Bowing of legs
 - c Epulides
 - d Cysts
 - e Localized pain

XIII EXAMINATION OF PATIENT

A HYPOPARATHYROIDISM

- 1 History
 - a Patient may have no symptoms
 - b Tingling or numbness of
 - (1) Face
 - (2) Lips
 - (3) Extremities
 - c Mental depression marked anxiety
 - d Failing vision
 - e Convulsive or tetanic seizures
 - f Retarded development if disease occurs during growth period
- 2 Physical status
 - a Hair—for alopecia
 - b Eyes
 - (1) Cataracts
 - (2) Photophobia
 - (3) Keratoconjunctivitis
 - c Teeth—structural defects (see 37 VI F)
 - d Neuromuscular tests
 - (1) Chvostek
 - (a) Skin over middle branch of facial nerve (anterior to external auditory meatus) is tapped lightly with
 - [1] Finger
 - [2] Percussion hammer
 - [3] Pencil or pen

- (b) Positive sign is a quick contraction of
 - [1] Entire lower portion of face
 - [2] Side of upper lip only

- (2) Trousseau
 - (a) Tourniquet or sphygmomanometer cuff is placed around upper arm
 - (b) Pulse need not be obliterated, but pressure equivalent to diastolic pressure should be maintained for 5 min
 - (c) Typical main en griffe or main d'accoucheur indicates a positive test
 - (d) Same test may be applied to lower extremities

- (3) Erb
 - (a) Median nerve in adults or peroneal nerve in children is stimulated by an electrical current
 - (b) The neuromuscular response to galvanic stimulation is obtained with weaker currents in tetany than in normal individuals
 - [1] Judgment and experience in performance of the test are necessary hence it is of limited value
 - [2] Children under 5 years are less responsive

- (c) Positive reaction to stimulation
 - [1] Muscles contract by cathodal opening current of less than 5 milliamperes
 - [2] Anodal opening current is less than anodal closing current (less current is required to obtain a response on opening the circuit when the positive electrode is applied than if the circuit is closed)

- (4) Schlesinger
 - (a) The leg is held at the knee

and is forcibly flexed at the hip joint

(b) Positive test—if extensor spasm occurs at the knee joint with plantar flexion of the foot

(5) Pool—positive result if carpal spasm develops with forced abduction of the arm

(6) Lust—tapping peroneal nerve results in muscular contraction

(7) Escherich—tapping at the angle of the mouth causes forward propulsion of the lips

(8) Schultz—tapping the tongue produces a concave upper surface

(9) Weiss—tapping the temporal branch of facial nerve results in contraction of the following muscles

(a) Frontal

(b) Orbicular

(c) Superciliary

(10) Hoffman—mechanical irritation of trigeminal nerve may elicit local pain

3 Laboratory data—findings are usually negative, except the following

a Sulkowitch test (see 36 \III B 4 a)

(1) Negative

(2) No calcinuria if serum calcium is below 7 to 8 mg % occasional exceptions

b Serum protein, albumin and globulin should be checked if any reason exists to question the calcium and phosphorus levels (see 103 \ G)

c Serum calcium

(1) Below 9 mg % usually rarely lower than 5 mg %

(2) Between 9 to 10 mg % some times in true hypoparathyroidism in which case the serum phosphorus is high

d Serum phosphorus

(1) Above 4 mg % in majority of cases

(2) If equivocal findings take fasting sample or one at least 6 hrs after eating

■ Basal metabolic rate and plasma cholesterol are done in patients with history of previous hyperthyroidism

4 Roentgenographic findings¹

a Teeth—blunted roots in cases beginning in childhood

■ Bones—osteomalacia is possible if parathyroid deficiency starts in childhood

B HYPERPARATHYROIDISM

1 History

a No symptoms

b Renal

(1) Colic

(2) Stones

(3) Sand

(4) Polyuria

c Polydipsia

d Bone pain

e Spontaneous fracture

f Muscular hypotonia

g Unexplained

(1) Fatigue

(2) Anorexia

(3) Vomiting

2 Physical status

a Extremities

(1) Various abnormalities

(2) Fractures

b Spine

(1) Round back

(2) Scoliosis

(3) Kyphosis

c Eyes—special examination by ophthalmologist may reveal specific changes (see 37 VI F)

d Teeth—occasionally malposed

e Neck—tumor may be palpable in lateral aspects of thyroid in rare instances

f Chest may be deformed

3 Laboratory data

a Sulkowitch test (see below)

b Serum calcium

(1) Over 11 to 18 mg % usually

(2) If normal and other evidence is strong Ellsworth Howard test may be performed and should be negative (see 36 \III B 4 b)

c Serum phosphorus

(1) Fasting level should be determined

(2) Level below 4 mg % usually

(3) Concentration should be less than 3 mg % to be significant unless renal damage is found

- d Alkaline phosphatase
- (1) Normal, if no bone pathology
 - (2) Values over 5 Bodansky units indicate bone changes which are proportional to degree of activity
- 4 Methods for special procedures
- Sulkowitch test⁴
- (1) Purpose
 - (a) In patients with tetany, the presence of more than a trace of urinary calcium is against hypocalcemia, with rare exceptions
 - [1] Possibly low renal threshold for calcium excretion
 - [2] Renal infection⁴
 - (b) Regulation of medication in hypoparathyroidism by checking urine and adjusting dosage according to the results (The patient can do this)
 - (c) To rule out hyperparathyroidism in patients with
 - [1] Kidney stones or rare fixed bones
 - [2] Equivocal serum calcium and phosphorus values
 - (2) Method
 - (a) Five cc of urine specimen
 - (b) Two cc of Sulkowitch solution
 - (c) The speed (3 to 30 sec) of appearance and amount of precipitate (zero to 4 plus) are to be noted
 - (d) Test may be modified by a special low calcium diet for 5 to 7 days which includes no milk milk products or eggs but only the following
 - [1] Orange juice
 - [2] Rice
 - [3] Cream of wheat
 - [4] Bread
 - [5] Uneda biscuits
 - [6] Margarine
 - [7] Bacon
 - [8] Lean meat
 - [9] Potato
 - [10] Applesauce
 - [11] Bananas
 - [12] Tomatoes
 - [13] Salt and pepper
 - [14] Sugar
 - [15] Tea
 - [16] Coffee
- (e) Twenty four hr urine collected on last day of diet
- (f) Two hundred mg or more of calcium/24 hrs is probably abnormal but is not pathognomonic
- (3) Results
- (a) Negative test (no precipitate)
 - [1] Indicates hypocalcemia (less than 75 mg %)
 - [2] Rules out hyperparathyroidism
 - (b) Three to 4 plus (heavy white cloud) suggests hypercalcemia (greater than 105 mg %)
- b Ellsworth Howard test⁴
- (1) Purpose—to aid in diagnosis of hypoparathyroidism
 - (2) Method
 - (a) Two cc (200 units) of parathyroid extract is given intravenously to a fasting individual
 - (b) Phosphorus content of urine specimens is determined at hourly intervals for 3 hrs before the injection and 3 to 5 hrs after it
 - (3) Results of phosphate excretion
 - (a) Normal—increased
 - (b) True hypoparathyroidism—sharp rise and a quick fall
 - (c) Pseudohypoparathyroidism—slight or no change
 - (d) Hyperparathyroidism
 - [1] Probably no increase if glands secreting at maximum capacity (see 38 XIII B 1 a (4))
 - [2] No data available
- c Renal function tests—of value in connection with differential diagnosis of parathyroid disorders
- (1) Concentration test
 - (a) Purpose — to determine function of tubules
 - (b) Method

- [1] After supper and until procedure is over patient does not take any thing by mouth
 - [2] Bladder emptied on retiring and urine is discarded
 - [3] All urine voided during the night is saved including first passed in the morning and labeled No 1
 - [4] One hr later, patient voids specimen No 2 collected
 - [5] One hr after that voids again and No 3 specimen obtained
 - [6] All three specimens tested for specific gravity
- (c) Results
- [1] Normal—at least one urine sample should have a specific gravity between 1.025 and 1.032
 - [2] Severe impairment—specific gravity below 1.010 in all
- (2) Dilution test
- (a) Purpose—to evaluate function of tubules
 - (b) Method
 - [1] No breakfast
 - [2] Bladder emptied
 - [3] 1500 cc of water taken (9:00 A.M.)
 - [4] At 30 min intervals 8 urine specimens are collected
 - [5] From 12:00 NOON to 8:00 A.M. next morning all the urine is saved in one container
 - [6] Volume of each sample is measured
 - [7] Specific gravity determined
- (3) Phenolsulfonphthalein (PSP) test
- (a) Purpose—to test the ability of the kidneys to excrete the dye
 - (b) Method
 - [1] Patient takes 2 glasses (300 to 400 cc) of water
 - [2] Twenty min later, bladder emptied
 - [3] One cc of phenolsulfonphthalein dye injected either
 - [a] Intramuscularly
 - [b] Intravenously
 - [4] Urine specimens are saved after injection
 - [a] Intramuscular—1 hr 10 min and 2 hrs 10 min
 - [b] Intravenous—15 and 30 min
- (c) Results of dye excretion
- | | |
|---------------------|----------|
| [1] Normal | PER CENT |
| [a] 1st sample | 40-50 |
| [b] 2nd sample | 20-25 |
| [c] Total excretion | 60-75 |
-
- | | |
|----------------|----------|
| [2] Impairment | OF TOTAL |
| [a] Slight | 40-59 |
| [b] Moderate | 25-39 |
| [c] Marked | 11-24 |
| [d] Maximal | 0-10 |
- (4) Urea clearance
- (a) Purpose—to study total function of kidneys
 - (b) Method
 - [1] Patient should be fasting
 - [2] Patient voids discards specimen and records exact time
 - [3] Two glasses of water are taken
 - [4] Blood specimen drawn $\frac{1}{2}$ hr after test starts
 - [5] At end of an hour, patient voids again recording exact time
 - [6] Total urine specimen
 - [7] Number of cc of blood cleared of urea by 1 cc of urine/min is determined
- (c) Results
- [1] Normal—any figure above 40 cc of blood cleared by 1 cc of

- urine/min or 75 to 130 per cent
- [2] Nephritis—between 10 and 30 cc or below 50 per cent
- (5) Inulin clearance
- (a) Purpose—to check glomerular filtration
- (b) Method
- [1] Procedure can be started any time of day
- [2] Height and weight are taken to calculate surface area
- [3] Patient should be reclining
- [4] Patient takes a glass of water at 8 30 A.M. and every $\frac{1}{2}$ hr until test is finished
- [5] One half glass of milk and 1 slice of toast and butter at 9 30 A.M.
- [6] At 10 00 A.M. ($1\frac{1}{2}$ hrs after starting test) blood sample is taken
- [7] Ten Gm of inulin dissolved in 100 cc of sterile saline solution at body temperature is injected intravenously at the rate of 10 cc/min
- [8] Bladder is emptied 1 hr after completion of injection and specimen is discarded
- [9] Urine specimens 2 and 3 hrs after injection are measured accurately and timed
- [10] Blood samples are taken $1\frac{1}{2}$ and $2\frac{1}{2}$ hrs after injection of inulin
- [11] Analysis for inulin is made by colorimetric method
- (c) Results
- [1] Normal—for a surface area of 1.73 sq meters, the average clearance is about 120 cc/min (volume of glomerular filtrate)
- [2] Abnormal
- [a] Nephrosis — decreased slightly
- [b] Acute or subacute nephritis — decreased moderately
- [c] Chronic hemorrhagic nephritis—decreased markedly (20 cc or less)
- (6) Diodrast clearance
- (a) Purpose — total mass of functional renal tissue and rate of blood flow can be determined (tubular excretory mass is measured)
- (b) Method
- [1] Part one
- [a] Patient should be reclining during test
- [b] Height and weight are taken for calculation of body surface area
- [c] Breakfast of toast butter and $\frac{1}{2}$ glass of milk ■ taken at any convenient time
- [d] 1000 cc of water is taken 2 hrs before starting the test
- [e] 200 cc of water is given every half hour until the end of the test unless administration of fluid is contraindicated
- [f] Two hrs after a liter of water has been taken, blood and urine samples are collected
- [g] Five cc of 35 per cent diodrast is injected intravenously noting the exact time
- [h] Fifteen min after the injection bladder is emptied, urine is discarded and exact time is recorded

- [1] Blood is drawn 10 and 20 min after initial emptying of bladder, noting the time
- [2] Collect all urine excreted 10 min after initial emptying of bladder
- [3] Blood and urine specimens are analyzed for iodine
- [4] Part two
 - [a] Patient drinks 500 cc of water after above procedure
 - [b] Thirty min later 30 cc of 35 percent diodrast is injected intravenously
 - [c] Bladder emptied and urine is discarded
 - [d] Blood sample is collected 5 and 10 min after voiding observe exact time
 - [e] Collect urine specimen 20 min after emptying bladder record time accurately
 - [f] Blood and urine specimens are analyzed for iodine
- [5] Results
 - [a] Diodrast plasma clearance averages 566 cc of blood/min range from 424 to 754 cc/min
 - [b] Renal blood flow averages 940 cc of blood/min range from 710 to 1260 cc/min
 - [c] Tubular excretory mass averages 36 mg of diodrast iodine/min range is 25 to 47 mg/min
- d Hamilton Schwartz (H S) test¹⁰
 - (1) Indication—study of conditions in which hyperparathyroid activity might be present or suspected
 - (2) Method
 - (a) Standardized and especially prepared rabbit is required
 - (b) Calcium chloride (100 mg in 10 cc of water) is administered by stomach tube to the rabbit at beginning of test, 1, 3 and 5 hrs
 - (c) Patient's blood (30 cc) is injected into rabbit's thighs (15 cc into each)
 - (d) Calcium in the rabbit's blood is determined before the test and 7 to 15 min after last 2 doses of calcium
 - (3) Result—positive test if blood calcium increases at least 0.3 millimols/liter after the third or fourth administration of calcium chloride
- 5 Roentgenologic examination
 - a Teeth are checked for absence of lamina dura in cases of hyperparathyroidism with bone involvement
 - b Skull to find
 - (1) Changes in tables
 - (2) Bone cysts especially in maxilla
 - c Pelvis and long bones should be studied for abnormalities (see 38 VIII)
 - d Kidneys for
 - (1) Stones
 - (2) Calcification
- 6 Chemical analysis of renal stones
- 7 Bone biopsy to identify type of lesion

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FIG 273 NORMAL PARATHYROID GLAND
Note sinusoidal arrangement of cells i.e.
cords of cells with capillaries between them
(x 13)

SECTION 37

PRIMARY HYPOPARATHYROIDISM

SYNONYMS Apathyrosis, Hypoparathyrosis

I DEFINITION

A state caused by a deficient or absent secretion of the parathyroid glands which when of a sufficient degree results in tetany (Tetany is characterized by hyperexcitability of the nervous system, intermittent painful spasms of the muscles, and is not always due to hypoparathyroidism)

II APPEARANCE

Aside from the rare occurrence of patchy alopecia of head hair, cataracts and carpopedal spasm on effort, a patient with chronic hypoparathyroidism may present no special characteristics

III AGE

All also reported in newborn¹¹

A POSTOPERATIVE TYPE

Seen more frequently in adult females because greater incidence of thyroid disease

B IDIOPATHIC TYPE

Childhood, adolescence and after 40

IV SEX

Both females predominate

V MENTAL DEVIATIONS

A INTELLIGENCE

Normal

B RESPONSIVENESS

Slow when depressed

C OTHER ABNORMALITIES

Marked dejection in some cases, dementia, mania and psychoses reported^{12 17 7 31 54 71}

VI PHYSICAL STATUS

A NUTRITION

Normal

1 Weight

Decreased occasionally

2 Fat distribution

Normal

B HEIGHT

May be retarded in children

C EXTREMITIES (see 37 VII M)

1 Upper

Normal

a Hands

Normal

b Fingers

Normal

c Span

Normal

2 Lower

Normal

a Feet

Normal

b Toes

Normal

D SPINE

Normal

E INTEGUMENT

1 General

Normal or may be rough scaly hyperkeratotic

a Texture

Normal

b Temperature

May be absent

c Moisture

d Eruptions	Secondary to vitamin deficiencies, impetigo herpetiformis ⁴³
■ Pigmentation	Normal
f Color	Normal
g Nails ^{7 44 ■}	All may be affected hypoplastic deformed pitted, grooved ridged irregular may be seat of Monilia infection, in which case each one is not involved, transverse grooving may appear with treatment (see Fig 239)
2 Hair ^{7 3 ■ ■}	
a Head	Patchy or total alopecia is rare premature graying
b Facial	May lose eyebrows and eyelashes
■ Axillary	May be absent
d Pubic	May be absent
■ Body	Normal
F HEAD	
1 Shape and size	Normal
2 Facial expression	Often dull
3 Eyes	
a General	Photophobia lacrimation (rare) ⁴⁶ keratoconjunctivitis, zonular or central cataracts are found (slit lamp may be necessary to detect these) ³⁴ may have diplopia
b Fundi	Normal optic edema or hemorrhage ^{47 48}
c Visual	
(1) Fields	Normal
(2) Acuity	Decreased with optic edema or cataracts
4 Ears and nose	Normal
5 Mouth and throat	
a General	Normal tongue and mucous membranes may show Monilia infection (see 36 I\ B 3) rhagades seen from secondary vitamin B deficiency (see Protocol 37, XVI)
b Teeth	Enamel defects ³⁹ transverse pitting occurs only during development but persists
c Larynx (voice)	Normal or may have indistinct speech during active tetany aphonia with chronic laryngeal spasm
G NECK	
1 General	Often thyroidectomy scar
2 Thyroid	Normal absent or goiter in India
H CHEST	Normal unless complications (see 37 VIII F 1)
I HEART AND PERIPHERAL VESSELS	
1 Heart	Normal may have beriberi heart
2 Rate and rhythm	Normal or increased rate
3 Blood pressure	Normal
4 Peripheral arteries and veins	Normal
5 Vasomotor	Normal
J BREASTS	
1 Male	Normal
2 Female	Normal
K ABDOMEN	
1 Liver	Normal unless congestive heart failure (see Protocol 37 XVI)
2 Spleen	Normal
3 Hernia	None
4 Tumor	None

L GENITALIA**1 Male**

- a Penis Normal
- b Testes Normal
- c Prostate Normal

2 Female

- External Normal
- b Internal Normal

M NEUROMUSCULAR**1 Muscles**

Gro sly normal but hyperirritable, especially on exertion

- a Positive Chvostek's sign (see 36 VIII A 2 d (1)) when untreated or insufficiently treated in rare cases (see Protocol 37, VVV) hyperirritability may not be demonstrated clinically except possibly by Erb's sign (see 36 VIII A 2 d (3))
- b Carpopedal spasm may be present at rest or on effort in subacute or chronic untreated stage, or elicited by Trousseau's sign (see 36 VIII A 2 d (2), Fig 241)
- c Abdominal muscles may be rigid with acute tetany
- d Spasm of anal sphincter
- e Isolated muscular twitchings may occur
- f Opisthotonos occasionally in children
- g See characteristics of acute tetany (see 37 VII A)

2 Gait

May be hampered by muscular spasm in severe cases

3 Body movements

Characteristic stance with sudden motion in some severe cases arms and few fingers are flexed or extended with slow athetoid movements

4 Tremor

None

5 Paresthesias

About lips, side of face and in extremities with or without active spasm, the latter indicating a very mild or latent state

6 Reflexes

Normal absent or increased

7 Petit mal attacks and convulsive seizures (see 37 VII IV B)**N SPEECH**

Normal unless laryngeal spasm

VII LABORATORY DATA**A URINE****1 General**

Normal

2 Special analyses

- a Sugar Normal
- b Albumin Normal
- c Nitrogen No data
- d Creatine No data
- e Creatinine No data
- f Sodium No data
- g Potassium Normal
- h Calcium Decreased negative Sulkowitch test if serum calcium is below normal threshold (see Chart 140 p 1474)
- i Phosphorus Decreased
- j Chloride No data
- k Iodine Normal¹⁹

B HEMATOLOGY**1 Red blood cells**

Normal

2 Hemoglobin

Normal

3 White blood cells

Normal

4 Differential

Normal

C BLOOD CHEMICAL ANALYSES

1 Sugar	Normal
2 Nonprotein nitrogen	Normal
3 Protein	
a Albumin	Normal or increased slightly
b Globulin	Normal or increased slightly
c A/G ratio	Normal
4 Uric acid	Normal or decreased
5 Cholesterol	Normal unless thyroid deficiency is also present then increased
6 Sodium	May be increased
7 Potassium	May be low in idiopathic type ²⁷
8 Calcium	Usually below 9 mg % (see Charts 79 and 82)
9 Phosphorus	Commonly above 4.0 mg %
10 Phosphate	Usually low decreased to 2 Bu in adults or 5 Bu in children
11 Chlorides	Normal or increased
12 Iodine	Normal ¹⁹
13 Creatine	No data
14 Magnesium	Decreased

D FUNCTION TESTS

1 Tolerance	
a Glucose	Normal
b Glucose insulin	No data
c Insulin	No data
2 Adrenal water test	Reported positive ⁴
3 Salt deprivation	No data (see 37 XIV)
4 Balance	
a Nitrogen	Normal

E MISCELLANEOUS TESTS

1 Basal metabolic rate	Normal
2 Circulation time	Normal
3 Sedimentation rate	May be increased
4 Specific dynamic action of protein	No data normal probably
5 Gastric analysis	Hydrochloric acid is increased or absent ²⁴
6 Electrocardiogram	QT interval may increase from 0.30 (normal) to 0.67 sec also changes in T waves (see Fig. 242) ^{9 30 41 58 64 69}
7 Spinal fluid	Normal or increased pressure ¹¹
8 Electroencephalogram	Alpha rhythm in occipital parietal and frontal area tend to disappear increase in beta rhythm is striking groups of 6 to 7 slow waves 2 to 3/sec treatment corrects but hyperventilation will again evoke changes in some cases ^{43 44 61 66}

F URINARY HORMONE ASSAYS

1 FSH	Insufficient data (see 37 XII B 7) ⁴³
2 LH	No data
3 Estrogens	Normal or low (see 37 XII B 7) ⁴³
4 Pregnenolol	No data
5 17 keto steroids	No data
6 11-oxysteroids	No data
7 Aschheim Zondek	No data negative probably
8 TSH	No data normal variations

G BIOPSY	
1 Endometrial	No data
2 Testicular	No data
H VAGINAL SMEAR	No data
I SEMEN ANALYSIS	No data

VIII ROENTGENOGRAPHIC FINDINGS

A SKULL

1 Cranial vault	Calcification in region of anterior horns and basal ganglia (see Fig 243) ^{27 38 61}
2 Sella turcica	Normal
3 Sinuses	Normal
4 Mandible	Normal
5 Teeth	Blunted roots if onset is during development ^{6 7}

II EPIPHYSEAL STATUS (bone age) May be retarded if onset is during development

C LONG BONES Normal or occasionally dense (see 37 VI)^{3 4}

D VERTEBRAE Normal

E BONE TEXTURE Normal, occasionally increased density,^{3 4} rarely osteomalacia in childhood

F MISCELLANEOUS

1 Chest Heart may be enlarged, may be fluid (see Fig 244)

IX ETIOLOGY

A SURGICAL

- 1 Removal of parathyroid glands due to hyperactivity
- 2 Following subtotal thyroidectomy^{43 63}

B CONGENITAL OR FAMILIAL^{43 63}

- 1 Aplasia
- 2 Transient neonatal hypofunction¹²
- 3 Moniliasis infection may be^{6 64}
 - a Cause since it usually precedes hypoparathyroidism
 - b Associated disease

C INFARCT

D IDIOPATHIC^{10 1 43 67 70}

E INFECTIONS

- 1 Syphilis
- 2 Tuberculosis
- 3 Measles
- 4 Otitis media
- 5 Influenza

F NONREACTIVITY OF END ORGANS TO PARATHYROID HORMONE (pseudohypoparathyroidism)

X PATHOLOGY

A GROSS—Parathyroids

- 1 Normal
- 2 Atrophy¹⁸

3 Fatty tissue

4 Cysts

B MICROSCOPIC

- 1 Parathyroids
 - a Normal tissue in pseudohypoparathyroidism⁵
 - b Hemorrhages observed in infantile tetany
 - c Atrophy
 - (1) Epithelial elements may be completely absent
 - (2) Fat globules
 - (3) Capsule and blood supply may remain
 - d Cysts
 - (1) Number—none to several
 - (2) Size
 - (a) Variable
 - (b) Some are 3 to 6 cm in diameter
 - e Fibrosis
 - f Inflammation from surrounding area
 - g Fatty degeneration²¹
 - h Hypoplasia¹
- 2 Pituitary—increased or absence of basophils has been reported^{1 40}
- 3 Adrenals
 - a Involvement rarely
 - b Absence of cortex²⁶
 - c Tuberculosis probable

- 4 Thymus
 - a Normal
 - b Scant¹
 - c Hyperplastic²
- 5 Brain
 - a Normal
 - b Calcification of²²
 - (1) Arteries
 - (2) Basal ganglia

XI PATHOLOGIC PHYSIOLOGY

A LOSS OF PARATHYROID HORMONE³ 37 38

- 1 Phosphate retention
- 2 Calcium in serum and extracellular fluid is low (see 36 VI B)
- 3 Absorption of calcium and all vitamins is poor
- 4 Osteoclastic activity is retarded causing decreased formation of osteoblasts
- 5 Ectodermal changes
- 6 Central nervous system alterations and convulsive seizures may be due to increased intracranial
 - a Fluid content
 - b Pressure

B PHYSICOCHEMICAL ALTERATIONS ASSOCIATED WITH TETANY

- 1 High serum phosphate (excess phosphate retention) with normal serum calcium may be produced in
 - a Animals with phosphate injections
 - b Newborns whose parathyroid function is inadequate and if cow's milk (excess phosphate) is given
- 2 Low serum calcium with
 - a High serum phosphorus (usual)
 - b Low serum phosphorus as in acute tetany after removal of parathyroid adenoma (see 38 VI)
- 3 Alkalosis from
 - a Increased consumption of sodium bicarbonate especially with poor renal function
 - b Overventilation can change reaction of blood from pH 7.4 to pH 7.9
 - c Excess vomiting and loss of hydrochloric acid producing an increase in
 - (1) Carbon dioxide combining power
 - (2) pH
- 4 Combined forms 3 a or 3 b alone or with 3 c
- 5 Factors aggravating existent parathyroid tetany (latent or manifest)

- a Allalosis (see above)
- b High serum potassium
- c Menstruation questionable relationship to sodium retention
- d Pregnancy
- e Lactation
- f High phosphorus intake
- g Sodium citrate
- h Avitaminosis D
 - 1 Mercurial diuretics¹
- j Acute infections
- k Exercise
- l Emotion
- m Vomiting
- n Diarrhea
- Cessation of medication in controlled tetany

6 Factors ameliorating parathyroid tetany (manifest or latent)—see Chart 78

- a Acid salts
- b Ferrous ammonium citrate
- c Calcium intravenous or oral
- d Dihydroxycholesterol
- e Vitamin D
- f Parathyroid hormone
- g Curare
- h Carbon dioxide inhalation questionable

1 Low serum potassium

7 Factors aggravating tetany of nonparathyroid origin

- a Alkalosis producing agents
 - (1) Sodium bicarbonate
 - (2) Sodium citrate possibly
- b Alkalosis producing disorders
 - (1) Pyloric obstruction with vomiting
 - (2) Emphysema
- c Renal insufficiency on account of phosphate retention
- d Menstruation
- e Pregnancy
- f High serum potassium

8 Factors tending to ameliorate manifest tetany from any cause

- a Acid salts
- b Calcium intravenously
- c Carbon dioxide inhalation
- d Low serum potassium

C MECHANISM OF TETANY

- 1 Theory—a decrease in ionized calcium in serum from any physicochemical alteration mentioned above produces

- decrease in ionized calcium of the tissues which is necessary to maintain normal function of nerves and tissues
- 2 The mechanism of this is unknown since tetany occurs under a variety of conditions in which the calcium or phosphorus content of tissue (extra cellular and intracellular) fluids cannot be determined
- 3 Tetany may be found with serum levels as follows
 - Normal calcium and phosphorus with alkalization of blood
 - b Normal calcium and high phosphorus
 - c Low calcium and high phosphorus
 - d Low calcium and low phosphorus
- 4 In hypoparathyroidism
 - Tissue fluids are certainly not saturated with calcium, although it is often deposited in cells (?) (i.e., cataracts, brain)
 - b However there is failure to calcify dentine and possibly bone during the growth period
- 5 Potassium depletion may prevent tetanic manifestations even with low serum calcium value
- 6 Many factors in tetany are still obviously obscure
 - (2) Transverse wrinkling of forehead
 - c Larynx
 - (1) Characteristic loud inspiratory crow
 - (2) Spasm may last minutes to hours
 - d Extremities (see Fig 240)
 - (1) Unilateral or bilateral involvement
 - (2) Carpal spasm ("obstetric hand"), may start on right side, if right handed
 - (3) Pedal spasm
 - (4) Adductor muscles of thighs may be affected
- 4 Deep reflexes may be increased
- 5 Convulsive seizures⁷⁸
 - a Epileptiform in many details and are mistaken for it
 - b Duration—a few seconds to hours
 - c Attack may start in hands and spread over whole body
 - d Any of the following may be observed
 - (1) Loss of consciousness
 - (2) Facial contractions producing distorted and freakish expressions
 - (3) Strabismus
 - (4) Inequality of pupils
 - (5) Nystagmus
 - (6) Chin may touch sternum
 - (7) Thick speech if conscious
 - (8) Biting of tongue
 - (9) Frothing at the mouth
 - (10) Difficulty swallowing
 - (11) Involvement of all smooth muscles
 - (12) Diaphragmatic spasm
 - (13) Cyanosis
 - (14) Severe cramplike pain in any or all muscles
 - (a) Tonic or clonic contractions
 - (b) Unilateral or bilateral
 - (c) Upper lower or all groups
 - (15) Spasm of heart muscle causing death
 - (16) Opisthotonos in children
 - e Deep sleep may follow
- 6 Mental symptoms
 - a Depression
 - b Anxiety

XII SYMPTOMATOLOGY

A ACUTE HYPOPARATHYROIDISM WITH TETANY

- 1 Introduction
 - a Acute hypoparathyroidism gives rise to tetany but the latter may also be caused by other disturbances
 - b The following signs and symptoms are not pathognomonic of acute hypoparathyroidism only
 - c Acute tetany may occur periodically in chronic hypoparathyroidism
- 2 Numbness and tingling of
 - Upper lip
 - b Side of face
 - c Extremities
- 3 Contractions of
 - Eyelids (blephorospasm)
 - b Facial muscles
 - (1) Corners of mouth may be drawn ('carp mouth') down with projection of nasolabial fold

- c Irritability
- d Dullness
- e Hallucinations
- f Loss of memory
- g Disorientation

B CHRONIC HYPOPARATHYROIDISM^{5 1 14 1} 4 6 64

- 1 Tetany may be
 - a Absent
 - b Latent—asymptomatic except under aggravating circumstances
 - Manifest—mild or moderate symptoms present constantly
 - d Acute—occurs in b or c under special circumstances
- 2 Neuromuscular
 - a Headache
 - b Visual disturbances
 - c Petit mal
 - d Mental changes
 - (1) Anxiety
 - (2) Depression
 - (3) Dementia
 - e Neurogenic bladder
 - f Paresthesias
- 3 Ectodermal
 - a Alopecia^{77 85 41 88}
 - b Skin—dry
 - c Nail growth retarded
 - d Dental defects (during growth period)
 - Cataracts⁴
- 4 Gastrointestinal
 - a Anorexia
 - b Diarrhea
 - c Constipation
- 5 Vitamin deficiencies
 - a Sore tongue
 - b Rhagades
 - c Cheriosis
 - d Tachycardia
 - e Dyspnea
 - f Edema
 - g Hemorrhagic tendency
- 6 Growth may be delayed
- 7 Sexual function
 - a Genital development may be retarded
 - b Amenorrhea
 - Loss of libido in males

XIII DIAGNOSIS

A PRIMARY HYPOPARATHYROIDISM WITH ACUTE TETANY

- 1 Occurrence to be watched for following
 - a Subtotal thyroidectomy
 - b Partial resection of hyperplastic parathyroids
 - c Removal of parathyroid adenomas
- 2 Symptomatology
 - a Onset may be
 - (1) Severe and sudden
 - (2) Mild with only
 - (a) Numbness
 - (b) Tingling
 - (3) Without symptoms, except for positive signs of
 - (a) Chvostek
 - (b) Trousseau
 - b Tingling or numbness of
 - (1) Face
 - (2) Lips
 - (3) Extremities
 - c Mental
 - (1) Depression
 - (2) Great anxiety
- 3 Physical status
 - a Chvostek's sign
 - (1) Positive
 - (2) Early finding but not always pathognomonic
 - b Trousseau's sign
 - (1) Positive
 - (2) Negative
 - c Carpopedal spasm
 - d Laryngeal spasm must be differentiated from
 - (1) Bilateral cord paralysis
 - (2) Pressure on trachea from postoperative
 - (a) Hemorrhage
 - (b) Edema
 - (3) Croup
 - (4) Diphtheria
 - Convulsive seizures with or without unconsciousness
- 4 Blood chemical analyses
 - a Calcium (serum)
 - (1) Rarely if ever below 4.5 mg %
 - (2) Usually below 8 mg %
 - Phosphorus (serum)
 - (1) Above 4 mg %

- (2) Exception after removal of parathyroid adenoma with high alkaline phosphatase may remain low

B PRIMARY HYPOPARATHYROIDISM WITHOUT MANIFEST OR LATENT TETANY

- 1 History is not very significant
- 2 Symptomatology
 - a None
 - b Failing vision
- 3 Physical status (see 37 VI)
 - a No abnormalities
 - b Cataracts
 - c Chvostek's and Trousseau's signs may be negative
- 4 Blood chemical analyses
 - a Calcium (serum) may be as low as 8 mg %
 - b Phosphorus (serum) may reach 5 mg %

C CHRONIC HYPOPARATHYROID TETANY

- 1 History
 - a Subtotal thyroidectomy — delayed tetany may be due to gradual loss of blood supply to parathyroids
 - b Operation for cataracts, especially in younger age group
- 2 Symptomatology—see 37 VII
- 3 Physical status
 - a Cataracts or evidence of previous iridectomy
 - b The following signs are positive (see 36 VIII)
 - (1) Chvostek, not pathognomonic
 - (2) Trousseau, may not be characteristically elicited
 - (3) Erb
 - (4) Pool
 - (5) Schlesinger
 - (6) Lust
- 4 Laboratory data
 - a Sulkowitch test is negative if serum calcium is below 7 to 8.5 mg %
 - b Calcium (serum)
 - (1) Is rarely if ever below 4.5 mg %
 - (2) May be only slightly decreased especially if serum phosphorus is high
 - c Phosphorus (serum)
 - (1) Is rarely below 4 mg %
 - (2) May reach 16 mg % or more (see Chart 81)

XIV DIFFERENTIAL DIAGNOSIS

A DISORDERS WITHOUT TETANY

The following are excluded as being the result of hypoparathyroidism when normal serum calcium and phosphorus values are present

- 1 Cataracts
- 2 Mental depression or psychoses
- 3 Diarrhea
- 4 Ectodermal defects
- 5 Vitamin deficiencies

B CONDITIONS WITH TETANY (latent or manifest)

- 1 Tetanus
 - a Characteristics
 - (1) Risus sardonius
 - (2) Lockjaw
 - (3) Rigidity of muscles
 - (4) Opisthotonos
 - (5) Tonic convulsive seizures
 - (6) Deep reflexes are hyperactive
 - (7) Profuse sweating
 - (8) Sensorium is perfectly clear
 - (9) Exhaustion
 - b Laboratory data
 - (1) Sulkowitch test—normal
 - (2) Normal serum
 - (a) Calcium
 - (b) Phosphorus
- 2 Avitaminosis D
 - a Occurrence
 - (1) Rickets
 - (2) Spasmophilia
 - (3) Osteomalacia
 - b Characteristics
 - (1) Skin lesions
 - (2) Cataracts are absent
 - (3) Signs of tetany may be present
 - (4) Bone deformities as in rickets
 - c Laboratory data
 - (1) Calcium (serum)
 - (a) Normal — normocalcemic hypophosphatemic type
 - (b) Decreased — hypocalcemic normophosphatemic type
 - (2) Phosphorus (serum) (see above)
 - (a) Normal
 - (b) Decreased
 - (3) Alkaline phosphatase (serum) — may be increased
 - d Roentgenographic findings — osteomalacia (see Fig 259, p 635)

- (2) Exception after removal of parathyroid adenoma with high alkaline phosphatase may remain low

II PRIMARY HYPOPARATHYROIDISM WITHOUT MANIFEST OR LATENT TETANY

1 History is not very significant

2 Symptomatology

- a None
- b Failing vision

3 Physical status (see 37 VI)

- a No abnormalities
- b Cataracts
- Chvostek's and Trousseau's signs may be negative

4 Blood chemical analyses

- a Calcium (serum) may be as low as 6 mg %
- b Phosphorus (serum) may reach 5 mg %

C CHRONIC HYPOPARATHYROID TETANY

1 History

- a Subtotal thyroidectomy — delayed tetany may be due to gradual loss of blood supply to parathyroids
- b Operation for cataracts, especially in younger age group

2 Symptomatology—see 37 VII

3 Physical status

- a Cataracts or evidence of previous incision
- b The following signs are positive (see 36 VIII)
 - (1) Chvostek, not pathognomonic
 - (2) Trousseau may not be characteristically elicited
 - (3) Erb
 - (4) Pool
 - (5) Schlesinger
 - (6) Lust

4 Laboratory data

- a Sulkowitch test is negative if serum calcium is below 7 to 8.5 mg %
- b Calcium (serum)
 - (1) Is rarely, if ever below 4.5 mg %
 - (2) May be only slightly decreased especially if serum phosphorus is high
- c Phosphorus (serum)
 - (1) Is rarely below 4 mg %
 - (2) May reach 16 mg % or more (see Chart 81)

XIV DIFFERENTIAL DIAGNOSIS

A DISORDERS WITHOUT TETANY

The following are excluded as being the result of hypoparathyroidism when normal serum calcium and phosphorus values are present

- 1 Cataracts
- 2 Mental depression or psychoses
- 3 Diarrhea
- 4 Ectodermal defects
- 5 Vitamin deficiencies

B CONDITIONS WITH TETANY (latent or manifest)

1 Tetanus

- a Characteristics
 - (1) Risus sardonius
 - (2) Lockjaw
 - (3) Rigidity of muscles
 - (4) Opisthotonos
 - (5) Tonic convulsive seizures
 - (6) Deep reflexes are hyperactive
 - (7) Profuse sweating
 - (8) Sensorium is perfectly clear
 - (9) Exhaustion
- b Laboratory data
 - (1) Sulkowitch test—normal
 - (2) Normal serum
 - (a) Calcium
 - (b) Phosphorus

2 Avitaminosis D

- a Occurrence
 - (1) Rickets
 - (2) Spasmophilia
 - (3) Osteomalacia
- b Characteristics
 - (1) Skin lesions
 - (2) Cataracts are absent
 - (3) Signs of tetany may be present
 - (4) Bone deformities as in rickets
- c Laboratory data
 - (1) Calcium (serum)
 - (a) Normal — normocalcemic hypophosphatemic type
 - (b) Decreased — hypocalcemic normophosphatemic type
 - (2) Phosphorus (serum) (see above)
 - (a) Normal
 - (b) Decreased
 - (3) Alkaline phosphatase (serum) — may be increased
- d Roentgenographic findings — osteomalacia (see Fig 259, p 635)

- (5) Blood pressure
 - (a) Normal
 - (b) Elevated
- (6) Genito urinary pathology
 - (a) Polycystic kidneys
 - (b) Congenital urinary obstruction
- (7) Osteoporosis may be absent
- Laboratory data
 - (1) Urine
 - (a) Albumin—variable amounts
 - (b) Sulkowitch test—negative
 - (2) Nonprotein nitrogen (blood)—increased
 - (3) Calcium (serum)—low, 5 to 7 mg %
 - (4) Phosphorus (serum)—high, 10 to 20 mg %
 - (5) Phenolsulfonphthalein test—decreased renal function

C CHRONIC NEPHRITIS

- 1 Characteristics
 - a Tetany signs are rare (see Protocol 37, XXVII)
 - b Compensating parathyroid hyperplasia and acidosis usually counteract
 - (1) Phosphorus retention
 - (2) Hypocalcemia
- 2 Laboratory data
 - a Urine—evidence of chronic nephritis
 - b Nonprotein nitrogen (blood)—elevated
 - c Calcium (serum)—may be
 - (1) Normal
 - (2) Low
 - (3) Elevated
 - d Phosphorus (serum)—increased
- 3 Roentgenographic finding—osteoporosis if disease of sufficient duration

D NEPHROSIS^a

- 1 Characteristics
 - Tetany—absent (ionized or diffusible calcium ■ normal)
 - b Growth—normal
- 2 Laboratory data
 - a Urine
 - (1) Albumin—markedly increased
 - (2) Calcium—decreased
 - b Cholesterol (plasma)—increased
 - c Calcium (serum)—low due to decreased serum protein
 - d Phosphorus (serum)—variable

- e Phosphatase (serum)—normal
- f Fecal calcium excretion—increased
- 3 Roentgenographic findings—long bone shafts show slight decalcification cause is obscure

E EPILEPSY

- 1 Occurrence
 - a Idiopathic
 - b Brain tumor
 - c Other intracranial lesions
- 2 Characteristics
 - a No signs of tetany (except possibly from overbreathing in some cases)
 - b Epilepsy may be
 - (1) Coexistent with hypoparathyroidism
 - (2) Aggravated by tetany
 - c Aura—present
 - d Evidence of tongue bite are often present
 - e Unconsciousness in grand mal
 - f Loss of sphincter control
 - g Unilateral contractures
 - h Opisthotonos—absent
 - i Choked disks may be present (also in tetany)
- 3 Laboratory data
 - a Calcium and phosphorus (serum)—normal
 - b Electroencephalogram (see 37 VII E 8)
 - (1) Normal
 - (2) Abnormal
- 4 Roentgenographic finding—skull may be abnormal

F MUSCULAR CRAMPS

- 1 Occurrence
 - At rest
 - b During sleep
- 2 Characteristics
 - a Only one lower limb usually involved at a time
 - b Elderly people more frequently affected
- 3 Laboratory data—normal

G IDIOPATHIC CHVOSTEK'S SIGN^a

- 1 Neuromuscular hyperexcitability as shown by positive Chvostek's sign
- 2 No other abnormalities of any kind demonstrable
- 3 Incidence—found in about 5 per cent of routine medical patients

(c) Notes

- [1] Avoid extravasation about vein for it causes sloughing
- [2] Prompt relief of symptoms, effects last about 1 to 2 hrs
- [3] Continuous intravenous drip unnecessary rarely indicated after removal of parathyroid adenoma (see 38 XVI C5)

- b Results—excessive intake of calcium lowers serum phosphate by
- (1) Increased fecal excretion
 - (2) Deposition in bone

3 Parathyroid hormone

a Dosage

- (1) Intramuscular or subcutaneous
 - (a) Initial—50 to 100 units (1 cc = 100 units)
 - (b) Maintenance—10 to 20 units daily until effect of A T 10 or vitamin D occurs
- (2) Intravenous—20 units or more
- (3) Notes

- (a) Intravenous injection may give dramatic response but usually need not be used
- (b) Maximum effect in 8 to 24 hrs peak in 15 hrs
- (c) Serum calcium level should be watched

b Results

- (1) The following are increased
 - (a) Phosphate excretion (urinary)
 - (b) Calcium absorption
- (2) Ineffective sometimes (see 37 XVI C 5)

4 Dihydratichysterol (A T 10)³⁶

a Dosage

- (1) Oral—2 to 5 cc/24 hrs (1 cc = 125 mg)
- (2) Notes
 - (a) Full effect evident in several weeks
 - (b) Calcium may also be given

b Results

- (1) Urinary phosphorus excreted in greater amounts than with vitamin D^{1 48 0 3 68}
- (2) Calcium and phosphorus absorption increased

5 Vitamin D (see 103 XI)^{10 60}

a Dosage

- (1) Oral—100 000 to 400,000 international units a day (20,000 to 40,000 international units/mg)
- (2) Notes
 - (a) Calcium may be given with it
 - (b) Full effect in several weeks
 - (c) Nontoxic usually (see 103 XI for overdosage)^{3 60}

b Results

- (1) Similar to A T 10
- (2) The serum phosphorus drop is not entirely due to a rise in serum calcium from increased absorption, but partly by a direct action of vitamin D on phosphorus excretion
- (3) This effect apparently does not occur readily if medication is given intramuscularly³³

6 Miscellaneous

- a Tracheotomy or laryngeal intubation may be indicated for severe laryngeal spasm
- b Avoid large quantities of milk during acute tetany because of its high phosphorus content, especially following removal of parathyroid adenoma in patients with⁹
 - (1) Extensive bone changes
 - (2) Very high serum phosphatase

II CHRONIC HYPOPARATHYROID TETANY

1 Calcium preparations

- a Calcium lactate or gluconate—1 or 2 teaspoonfuls (20 to 60 Gm) 3 or 4 times a day
- b Calcium chloride—30 per cent solution is suitable 2 to 4 teaspoonfuls well diluted with hot water or palatable liquid 3 to 6 times daily or enteric coated capsules in corresponding amounts

c Notes

- (1) Calcium lactate is preferred because it is better tolerated
- (2) Sufficient to control mild tetany
- (3) Albright and Reifenstein warn against long continued calcium chloride therapy⁸

2 Dihydratichysterol (A T 10)^{4 60}

- a Oral—½ to 2 cc daily or every other day (1 cc = 125 mg)

- b Maintenance—to be determined by checking serum calcium levels
- Notes
 - (1) More efficient than vitamin D¹
 - (2) Adequate calcium intake advisable
- 3 Vitamin D (less expensive)
 - a Oral—50 000 unit capsules from 2 a week to 4 a day doses up to 500 000 daily have been reported (see 103 \I)
 - b Maintenance—dependent on serum calcium
 - Note—calcium should also be prescribed
- 4 Parathyroid hormone unnecessary
- 5 Amphogel
 - a Indication—rarely needed
 - b Dosage, oral—120 to 160 cc daily
 - c Result—phosphate absorption reduced
- 6 Ammonium chloride¹⁹
 - a Indications
 - (1) Helpful in mild cases along with the administration of calcium lactate
 - (2) Theoretical value in tetany of alkalosis
 - b Dosage oral—1 to 2 Gm t i d
- 7 Thyroid (desiccated USP)
 - a Indications
 - (1) If tetany follows subtotal thyroidectomy
 - (2) For thyroid deficiency
 - b Dosage oral—2 gr (maximum dose) daily if tolerated
- 8 Diet
 - a Low phosphate
 - (1) Intake of 0.3 to 0.5 Gm a day is optimal
 - (2) Theoretically advisable but it is tiring and usually discarded by patients
 - (3) Avoidance of milk is sufficient
 - (4) Phosphate absorption lowered (questionable)
 - b High acid ash intake decreases
 - (1) Blood alkalinity
 - (2) Irritability of
 - (a) Nerves
 - (b) Muscles
- 9 General
 - a Vitamins if evidence of their deficiency
 - b Cataracts
 - (1) Do not develop if blood calcium is kept normal
 - (2) Should be removed when indicated
 - Changes in medication should not be made oftener than at 2 to 3 week intervals unless
 - (1) Signs of tetany are present
 - (2) Revulsion for calcium develops
 - (3) Nausea vomiting and/or headache occur
 - d Sulkowitch test by patient for daily urinary excretion of calcium
 - (1) If test is negative or slightly positive dosage of A T 10 or vitamin D is adequate
 - (2) If test is strongly positive patient may be receiving too much of either medication
 - e For a long range treatment determination of serum calcium and phosphorus is more reliable than the use of the Sulkowitch test chiefly because of a variable renal threshold for calcium in hypoparathyroidism⁶⁰

XVII PROGNOSIS

A GENERAL

- 1 Excellent with adequate treatment
 - a Cataracts do not
 - (1) Develop
 - (2) Progress
 - (3) Recede
 - b Trousseau's sign disappears
 - c Chvostek's sign may remain but usually is not found with adequate therapy
- 2 Occasionally hypoparathyroidism is difficult to control
- 3 Complications develop in
 - a Untreated patients
 - b Long standing cases (see 37 \V)

XVIII CAUSES OF DEATH

A NATURAL CAUSES MOST COMMON

B CEREBRAL

- 1 Edema
- 2 Hemorrhage—theoretically possible

C SPASM

- 1 Cardiac
- 2 Diaphragmatic
- 3 Laryngeal

D CONGESTIVE HEART FAILURE (rare)

PRIMARY IDIOPATHIC HYPOPARATHYROIDISM WITH CATARACTS, BUT WITHOUT TETANY

PROTOCOL XXV

Family history Negative*Past medical* Only illness diphtheria at 17*Chief complaints* Diminished vision from bi lateral cataracts for 18 months*History of present illness* Deafness in right ear which patient says is congenital for his grandfather and sons have it. Some stiffness of joints*Physical examination* Age 59, male married, 3 children Weight 180 lbs Height 73 in with shoes Pulse 60 BP 110/80 Early arcus senilis and bilateral cataracts Slight colloid changes in thyroid Chvostek's and Trousseau's signs negative Vital capacity 3 600 cc

Laboratory data RBC 4,700,000 Hgb 96%
WBC 6,550 Differential polymorpho
nuclears 65%, lymphocytes 27%, mono
cytes 6.5%, eosinophils 1.5% Coagulation
time 6, 12, 12 15 min Firm clot re
traction Sugar 98 mg %, 4 hrs after eat
ing NPN 35 mg % Uric acid 3.0 mg %
Total protein 7.09 Gm % Serum calcium
6.6 mg % Serum phosphorus 4.3 mg %,
4 hrs after eating BMR minus 9%

Röntgenographic findings Calcium content of bones normal*Treatment* Patient had cataracts removed 30 gr calcium and parathyroid hormone 1/10 gr were prescribed elsewhere*Progress and Treatment*

MONTHS	CALCIUM MG %	PHOSPHORUS MG %	THERAPY
5	6.5	5.3	Calcium lactate 6 heaping teaspoonfuls daily
6	7.0	4.7	As above
8	10.5	4.2	As above and viosterol 3 drops t.i.d.
10	7.0	4.5	As above but viosterol stopped
17	9.2	4.4	As above
29	7.9	4.4	Medication taken irregularly

Comment An unusual case of hypocalcemia without a demonstrable cause and no manifest or latent tetany by the ordinary clinical tests. The ease with which the serum cal

cium rose with calcium and viosterol and the elevated serum phosphorus favors the diagnosis of hypoparathyroidism

HYPOPARATHYROIDISM

PROTOCOL XXXI Figs 242, 244

Primary idiopathic hypoparathyroidism with secondary multiple vitamin deficiencies beriberi heart (?) with congestive failure, cataracts unilateral seizures (tetany)

Family history Negative*Past medical* Cataracts (bilateral) removed at age of 32. Patient denied any physical or mental symptoms prior to or since cataract operation until present illness. Diet has been normal in all respects*Chief complaint* Spasm of extremities*History of present illness* Sudden fall with loss of consciousness and later stiffness of right arm. Increasing shortness of breath orthopnea and edema of ankles. Recurring spasms of left arm and leg beginning 9 months previously about once a week and increasing to once or twice daily. Similar attacks began on right side 4 months previ

ously and continued 1 or 2 times a day having disappeared on left side. Dilantin sodium diminished the number of attacks. Fourteen days before admission forceful vomiting occurred after breakfast without any previous nausea. He could eat and retain another meal after this. Loss of energy and libido. Mental depression but memory normal

Physical examination Age 44 male married Slightly cyanotic patient with a rather dull masklike expression sitting in bed and breathing with some difficulty. Weight 136 lbs Pulse 90 BP 80/60 to 110/60. Seborrheic dermatitis. Defective nails. Patchy loss

of head hair Irregular pupils from previous iridectomy, corneal injection Fundi showed early edema central and nasal portions of disks blurred and no hemorrhages Cheilosis and rhagades Thyroid normal Heart rhythm regular, no murmurs Flatness at both lung bases, indicating fluid Vital capacity 1000 cc Circulation time 24 sec Chvostek's sign positive bilaterally Knee and ankle jerks absent Tremor of lips and tongue Ataxia with finger to nose test Left biceps reflex greater than right Abdominals absent Romberg's sign positive

Laboratory data Urine—specific gravity 1.015 to 1.028, epithelial cells, albumin present sugar absent calcium 37 mg/24 hrs RBC 4,900,000 and 5,200,000 Hgb 14.5 Gm WBC 10,700 to 11,000 Differential polymorphonuclears 68%, lymphocytes 28% eosinophils 4% Hematocrit 47% Prothrombin time (during treatment) 72% of normal NPN 10 mg % Total protein 7 Gm %, albumin 4 Gm % globulin 3 Gm % Serum calcium 4.1 mg % Serum phosphorus 9.0 mg % Sodium chlorides 693 mg % Serum alkaline phosphatase 3.4 Bu Carbon dioxide combining power 34 volumes % PSP (intravenous) 31% in 1 hr (74% normal) Bromsulphthalein dye 10% retained Spinal fluid pressure 300 mm of water Sedimentation rate 38 mm/hr Electrocardiogram, see Fig 242

Röntgenographic findings Bones normal in texture and calcium content Chest—some cardiac enlargement pleural effusion (see Fig 244) IV pyelogram normal

Treatment Bilateral chest tap 1300 cc and 1100 cc (1,700 mg total protein) High vitamin diet Intravenous B complex daily Sodium citrate was given with apparent drop in serum calcium (A convulsive seizure occurred at this point consisting of a peculiar aura with flexion contracture of forearms and extension of fingers Loss of consciousness lasting about one minute this was not tetanic but cerebral in origin) A T 10—5 cc for 6 days then 10 cc for 6 days (serum calcium rose to 8.2 mg %) Vitamin D 100,000 units daily Calcium lactate 2 teaspoonfuls t i d

Progress Discharge from hospital—remarkable relief of all symptoms and signs Vital capacity 200 cc Weight 115 lbs

MONTHS

- 2 Marked improvement. No dyspnea or edema Frequency Drinks 3 to 4 quarts of liquids daily Weight 124 lbs Pulse rate 96 Chest film—lungs and heart normal Nails regrowing Skin only No rhagades Some infection of sclerae Reflexes absent Fundi normal Serum calcium 11.3 mg % Serum phosphorus 3.4 mg % Vitamin D 150,000 units daily Vitamin B complex capsules b i d Calcium—2 teaspoonfuls t i d
- 4 Serum calcium 9.3 mg % Serum phosphorus 3.3 mg % On same regimen, except 100,000 units of vitamin D daily To stop this medication, and continue with calcium and vitamin B
- 6 Chvostek's sign positive Serum calcium 7.2 mg % Serum phosphorus 5.2 mg % Spinal fluid calcium 4.5 mg % Restarted vitamin D, 200,000/24 hrs Vitamin B stopped
- 8 Serum calcium 7.0 mg % Serum phosphorus 4.9 mg % Serum chlorides 586 mg % Urea clearance 74% of normal Vitamin D omitted for 2 weeks
- 20 No complaints Weight 157 lbs BP 102/78 Pulse 72 Vitamin D and calcium continued
- 39 Nails are normal now Still has some erythema on his face Chvostek's and Trousseau's signs are positive BP 110/80 Excellent health Serum calcium 8 mg % Serum phosphorus 2.8 mg % Sulzowitch test Grade 2 EKC normal Chest film—no change since last examination No calcium for 8 months To take 100,000 units of vitamin D daily again

Comment A case of primary idiopathic hypoparathyroidism causing cataracts for which an operation was necessary about 10 years ago Onset of tetanic manifestations 9 years or so later This disorder probably interferes with vitamin absorption from the gastrointestinal tract or their utilization is retarded The prompt reaction to vitamin B injections suggests that the latter thesis is unlikely

TETANY ASSOCIATED WITH POLYCYSTIC KIDNEYS AND UREMIA ABSENCE OF PARATHYROID HYPLRPLASIA AND BONE CHANGE*

PROTOCOL XXVII

Past medical Accepted for insurance 3 years before admission

History of present illness One year previously, patient noted tingling on both sides of his face and fingers at time of an acute infection. This gradually disappeared. Four weeks before the first examination he had anorexia, progressive pallor, weakness and severe cramps in legs lasting 2 min or more.

Physical examination Age 30 years, male BP 130/70. Marked pallor. Fundi negative. Positive Chvostek's and Trousseau's signs. Kidneys not palpable.

Laboratory data Urine—albumin 2 plus specific gravity 1.010. Bence Jones negative. Sulkowitch negative. RBC 2,190,000. Hgb 5.9 Gm. WBC 8,500. NPN 175 mg %. Serum protein 8.2 Gm %. Serum calcium 4.4 mg %. Serum phosphorus 9.5 mg %. Carbon dioxide combining power 19 vol %. Serum chlorides 372 mEq %. Sedimentation rate 75 mm/hr. Subsequent serum total protein 6.3 Gm %, albumin 5.35 Gm %, and globulin 1.00 Gm %.

*We are indebted to the pathologic department of the Beth Israel Hospital, Boston, for the autopsy report.

Röntgenographic findings Skull negative. No change in bone structure or decalcification.

Treatment and course Patient transferred to Beth Israel Hospital for possible treatment with peritoneal lavage. His course was progressively downhill.

Postmortem examination Kidneys—small bilaterally polycystic, right larger than left and dilatation of one ureter presumably on congenital basis, chronic pyelonephritis. Parathyroids—only one identified, fat absent, chief cells exclusively present, size 0.5 x 0.3 cm. Interpretation—possibly prehyperplastic state but not hyperplasia on account of size and arrangement of cells. Remainder of postmortem examination essentially negative.

Comment The rapid termination and history indicate uremia of fairly short duration. The symptoms 1 year prior to admission suggest latent tetany. This may have been held in check by developing acidosis. If significant renal failure had been present long enough, parathyroid hyperplasia should have been found. Failure of hyperplasia may have been due to pre-existing hypoparathyroidism.

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FIG 239 EVIDENT CHANGES IN NAIL BEDS IN IDIOPATHIC PRIMARY HYPOPARATHYROIDISM (See Fig 243) Grooved fingernails which appeared during initial period of treatment with dihydrotachysterol (AT 10) and calcium These eventually grew out



FIG 240 HYPOPARATHYROIDISM (See also Chart 82) Tetanic seizure in severe and untreated hypoparathyroidism (postoperative) This seizure was produced simply by rising from a sitting position



FIG 241 TROUSSEAU'S SIGN IN TETANY. Elicited by from 3 to 5 minute application of sphygmomanometer cuff obliterating pulse (Swinton N W Postoperative parathyroid tetany New England J Med 217 165 169)

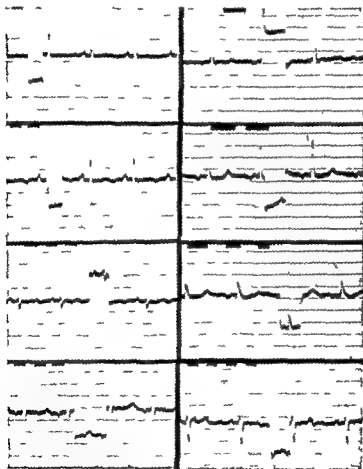


FIG 242 HYPOPARATHYROIDISM (See also Protocol 37 XVI and Fig 244) Electrocardiogram in idiopathic hypoparathyroidism. Congestive heart failure was found. Tracings (left) before therapy (right) after AT 10 and calcium was administered. Note the rise in T waves change in direction of E waves in leads II and III. Part of these changes may be related to vitamin deficiency which was thought to be present. The common change in hypoparathyroidism is lengthening of Q-T interval

FIG 243 IDIOPATHIC HYPOPARATHYROIDISM (See also Fig 239) Age 39 Bilateral calcification in ventricles Four year history of increasing fatigue loss of libido headaches tinnitus without deafness visual disturbance numbness in face and extremities unsteady gait slow speech and inability to concentrate Positive Chvostek's and Trousseau's sign Eye examination revealed changes consistent with hypoparathyroidism (Sulkowitch test negative) Serum protein 6.8 Gm % Serum albumin 4.7 Gm % Serum globulin 2.1 Gm % Serum calcium before treatment 5.1 and 6.2 mg % Serum phosphorus 4.4 and 5.1 mg % Serum alkaline phosphatase 2.6 B.U. Improvement marked on dehydrotachysterol and calcium Serum calcium 8.2 and 10.5 mg % Serum phosphorus 3.8 and 4.4 mg % on treatment The bizarre complaints lead frequently to a diagnosis of neurosis but the cerebral calcification raised the question of an intracranial lesion Oxygen encephalograms showed normal ventricular filling the calcification appeared to line the ventricular walls Calcification was noted in pelvic and leg arteries The finding of a low serum calcium and physical signs of tetany established the diagnosis after a 4 year illness

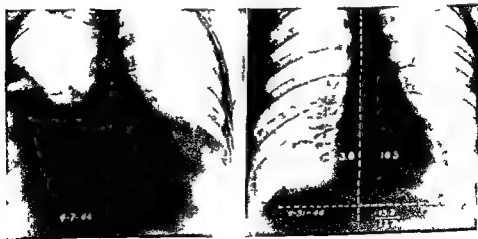


FIG 244 HYPOPARATHYROIDISM (See also Protocol 3, XVI and Fig 242) Heart in hypoparathyroidism before (left) and after (right) treatment Note fluid in chest and larger heart shadow on left Patient has remained well on vitamin D and calcium for 3 years

BALANCE +131 GM
SERUM Ca 63-79 MG %

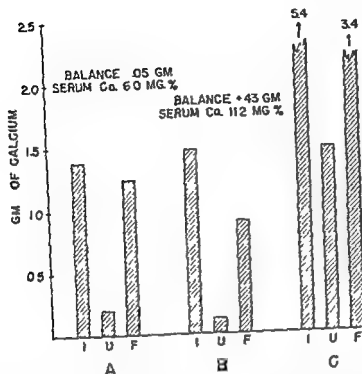


CHART 18 HYPOPARATHYROIDISM WITH TETANY. Effect of calcium and parathyroid extract on levels of serum urinary and fecal calcium (I = intake of calcium U = urinary excretion F = fecal excretion)

(A) Effect of 1.39 Gm of calcium (approximate daily requirement in normal) given orally to a case of untreated parathyroid tetany considered to have no functioning parathyroid tissue. Duration of experiment 5 days. Note that a normal relationship was not produced between urinary and fecal calcium indicating that calcium administered was not absorbed. There was no significant change in serum calcium (> and < 4 mg %) or in serum phosphorus (10.7 and 10.1 mg %). No clinical improvement. Calcium balance expressed in grams was slightly positive although equivocal.

(B) Effect of parathyroid extract on this case with approximately same calcium intake. Note that serum calcium rose to a normal value. Symptoms of tetany relieved. This chart shows that more calcium was absorbed in relation to intake than in (A) suggesting a local effect of parathyroid hormone on gastro-intestinal tract. Urinary output of calcium is still not in normal relationship to fecal calcium. Calcium must have been retained. Serum phosphorus not recorded here fell to 5.4 mg % due to greater urinary excretion of phosphorus.

(C) Result of high calcium intake some time after cessation of parathyroid extract. Serum calcium had not yet returned to original value (A). No symptoms of tetany had reappeared at this level of serum calcium. There was only a slight change in serum calcium and phosphorus concentrations with the high calcium intake although the urinary excretion of calcium was greater. This observation suggests that an increased intake of calcium produces greater gastro-intestinal absorption. However the previous effect of parathyroid hormone may have persisted (no tetany higher serum calcium) and thus influenced absorption. Both a high and low phosphorus intake was tried without significant changes in serum calcium and phosphorus levels. Urinary phosphorus excretion was increased with greater phosphorus intake. Since tetany did not reappear it may be accounted for by an improved calcium phosphorus ratio or possibly the satisfactory tissue content of calcium irrespective of the serum calcium level.

It is to be conjectured that large oral doses of calcium alone will not relieve tetany when no functioning parathyroid tissue exists. Parathyroid hormone may facilitate calcium absorption as well as the level of serum calcium (Albright F and Ellsworth P. Studies on the physiology of the parathyroids. Calcium and phosphorus studies on a case of idiopathic hypoparathyroidism. J Clin Investigation 7: 183-201).

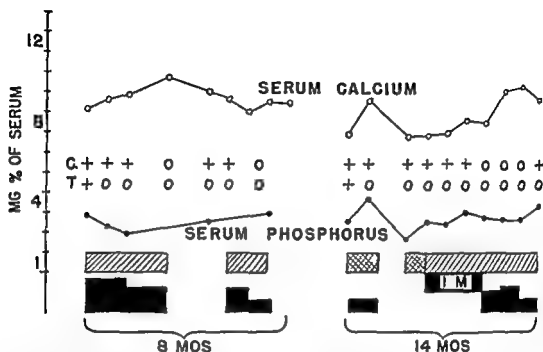


CHART 79 IDIOPATHIC HYPOPARATHYROIDISM Age 29 female Hypoparathyroidism with clinical tetany but with only slight change in serum calcium and phosphorus. Over a period of 9 years patient had intermittent stiffness of arms and facial muscles initiated by noise, confusion and emotion. Attacks lasted about an hour and she rarely had more than 2 to 3 spells each year. Thumbs adducted during attacks. Tingling of face and hands almost continuously. Eating habits normal. Positive Chvostek's and Trousseau's signs.

Serum calcium 9.1 mg % Serum phosphorus 4.0 mg % All signs of tetany disappeared on treatment with vitamin D and calcium. Serum calcium rose to 10.9 mg %. When 20 cc of 10% calcium gluconate was injected intravenously (Chart 80) the rise in serum calcium was slight as compared with the rise when on therapy. Note decreasing level of serum calcium 3 years later without treatment. Failure to obtain relief with intramuscular vitamin D 400,000 units 2 to 3 times a week is noteworthy. Ammonium chloride and calcium without vitamin D did not control tetany.

This case illustrates that vitamin D and calcium therapy in tetany may be of value when the usual low calcium and high phosphorus are not found.

Solid block represents vitamin D orally beginning with 150,000 units daily. I.M. indicates intramuscular vitamin D (Daratol). C means Chvostek's sign. T stands for Trousseau's sign. Plus = present, zero = absent. Single cross-hatched block represents calcium lactate 3 large teaspoonsful daily. Double cross-hatched area indicates ammonium chloride and calcium.

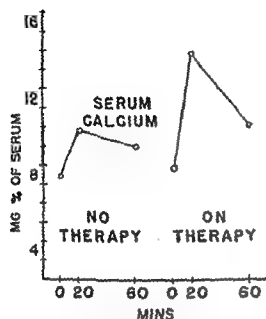


CHART 80 SERUM CALCIUM CURVES AFTER INTRAVENOUS INJECTION OF CALCIUM GLUCONATE (see Chart 79) (Left) Before vitamin D therapy (Right) While taking vitamin D and calcium orally

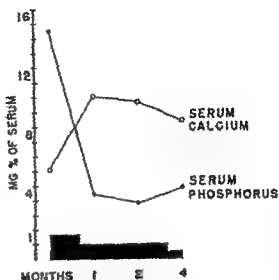


CHART 81 TETANY Postoperative hypoparathyroidism with tetany and unusually high phosphorus

Past medical Three operations for thyroid disease Unsuccessful therapy elsewhere with oral calcium until vitamin D administered

History Age 26 Frequent tetanic attacks and great lassitude Tetany worse following catamenia Parathyroid extract is said to have increased the exophthalmos

Laboratory findings NPN 24 mg % PSP 30% in 30 min The high serum phosphorus plotted in chart is average of 2 determinations (16.2 and 14.7 mg %)

Treatment Calcium lactate 3 heaping tea spoonfuls daily Vitamin D in doses of 150,000 units a day were given initially and finally reduced to 50,000 which as the chart shows was not adequate Vitamin D appears to have been as effective as dehydrotachysterol in mimicking the action of parathyroid hormone by producing an increased phosphorus excretion and a normal serum phosphorus

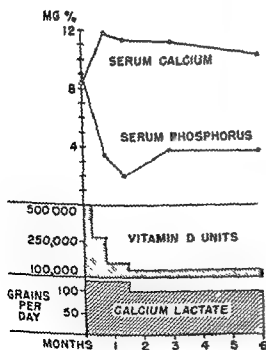


CHART 82 HYPOPARATHYROIDISM WITH TETANY (See also Fig 240) Vitamin D therapy in severe postoperative parathyroid tetany Note that serum calcium was only moderately depressed but that serum phosphorus was high Patient developed severe hypertension but renal function studies were normal The response to vitamin D and oral calcium gives evidence of adequate renal function for the serum phosphorus was decreased to 2 mg % There were no definite symptoms from hypercalcemia

SECTION 38

PRIMARY HYPERPARATHYROIDISM

SYNONYMS

Acute hyperparathyroidism
Parathyroid poisoning²

Hyperhyperparathyroidism
Chronic hyperparathyroidism

NOTE The following are actually complications and not synonyms
Osteitis fibrosa generalisata
Osteitis fibrosa cystica or von Recklinghausen's disease

I DEFINITION

A condition due to excessive parathyroid secretion with an increase in urinary excretion of calcium and phosphorus which may lead to formation of renal calculi and/or generalized decalcification, fibrocystic lesions or tumors of the skeleton

II APPEARANCE

Normal, except when marked bony deformities, as kyphosis scoliosis, fractures and distortion of the limbs are present (see Fig 245)

III AGE

From 10 to 80^{33 43 104} (greatest incidence of parathyroid adenomas is around 45 years), also in infants¹¹⁸

IV SEX

Females more often affected than males, ratio 3 or 4 : 1 (adenomas)^{23 9 104}

V MENTAL DEVIATIONS

A INTELLIGENCE

Normal

B RESPONSIVENESS

Normal

C OTHER ABNORMALITIES

May have delirium in acute type

VI PHYSICAL STATUS

A NUTRITION

Normal

1 Weight

Decreased often

2 Fat distribution

Not remarkable

B HEIGHT

May be decreased because of vertebral involvement (see 38 VIII D)

C EXTREMITIES

1 Upper

Normal unless bone deformities occur

a Hands

Normal

b Fingers

Normal clubbing has been reported^{1 7}

c Span

May be increased because of shrinkage of stature

2 Lower

Normal or may be bowed

a Feet

Normal

b Toes

Normal

D SPINE

Normal round back, kyphosis or scoliosis

E INTEGUMENT

1 General

Normal

a Texture

Normal

b Temperature

Normal

e	Moisture	Normal
d	Eruptions	Normal
e	Pigmentation	Normal
f	Color	Normal
2	Hair	
a.	Head	Normal
b	Facial	Normal
c.	Axillary	Normal
d	Pubic	Normal
e	Body	Normal
F	HEAD	
1	Shape and size	Normal
2	Facial expression	Normal
3	Eyes	
a	General	Normal slit lamp examination may reveal that conjunctivae of palpebral fissure area contain small glasslike particles ¹⁴³ presumably amorphous calcium deposits corneal changes consist of grayish granular epithelia and sub epithelial deposits running concentrically with limbus on either side or both, not pathognomonic of hyperparathyroidism for it is also found in other hypercalcemic conditions ⁶⁴ may be transient lesions in conjunctivae
b	Fundi	Normal
c.	Visual	
(1)	Fields	Normal
(2)	Activity	Normal
4	Ears and nose	Normal or may have calcium deposits in ear drums ⁴⁴ deafness may occur
5	Mouth and throat	
a	General	Normal or fibrous tumor of gums (epulides) seeded on jaw ¹ red tongue
b	Teeth	Malocclusion and disarrangement occasionally, may fall out ¹ ⁵ ¹²⁵
c	Larynx (voice)	Normal
G	NECK	
1	General	Parathyroid tumor may be palpated in 10 per cent ¹⁰⁴
2	Thyroid	Normal usually, may contain parathyroid adenoma
H	CHEST	May show deformity due to bent ribs and spinal curvature
I	HEART AND PERIPHERAL VESSELS	
1	Heart	Normal
2	Rate and rhythm	Normal
3	Blood pressure	Normal or elevated
4	Peripheral arteries and veins	May be sclerotic
5	Vasomotor	No data
J	BREASTS	
1	Male	Normal
2	Female	Normal
K	ABDOMEN	
1	Liver	Normal
2	Spleen	Normal
3	Hernia	None
4	Tumor	None

L GENITALIA

1 Male

- a Penis Normal
- b Testes Normal
- c Prostate Normal

2 Female

- a External Normal
- b Internal Normal

M NEUROMUSCULAR

1 Muscles

Hypotonus and decreased response to galvanic stimulation⁴⁸

2 Gait

Normal, unless hampered by bone pain or deformities

3 Body movement

Normal

4 Tremor

None

5 Paresthesias

If there is encroachment on nerves by bone softening

6 Reflexes

Normal

N SPEECH

Normal

VII LABORATORY DATA

A URINE

1 General

May be excessive in quantity (up to 12 1/24 hrs) and milky in appearance, calcium phosphate casts, especially with little or no albumin calcium sand, varying degrees of renal impairment pyuria and hematuria from pyelitis and/or pyelonephritis¹⁰

2 Special analyses

- a Sugar None
- b Albumin None, Bence Jones protein may be found
- c Nitrogen May be increased
- d Creatine No data
- e Creatinine No data
- f Sodium No data
- g Potassium No data
- h Calcium (see Chart 140) Increased (positive Sulkowitch test), 70 to 90 per cent of total calcium output occurs in urine (10 to 30% in normals) (see Chart 83) no excess in some cases when

(1) Kidney function is poor

(2) Due to questionable avitaminosis D with normal renal function¹²³

(3) Serum calcium is normal during a remission¹⁴⁵

i Phosphorus

Marked renal impairment may decrease output otherwise follows calcium excretion

j Chloride

May be increased

k Iodine

No data

B HEMATOLOGY

1 Red blood cells

Normal or may be increased due to hemoconcentration

2 Hemoglobin

Normal or may be increased due to hemoconcentration, anemia reported⁹

3 White blood cells

Normal

4 Differential

Normal

5 Coagulation time

Prolonged²³

6 Clot

Friable

C BLOOD CHEMICAL ANALYSES

1 Sugar	Normal
2 Nonprotein nitrogen	Increased, if sufficient renal impairment
3 Protein	May be elevated on account of hemoconcentration with low serum protein serum calcium may be normal
a Albumin	Normal
b Globulin	Normal
c A/G ratio	Normal
4 Uric acid	No data
5 Cholesterol	Normal
6 Sodium	Normal
7 Potassium	No data
8 Calcium	Above 10 to 16 or 17 mg %, rarely 20 mg %
9 Phosphorus	Decreased
10 Phosphatase (alkaline)	Normal or increased with bone involvement ³³
11 Chlorides	Normal or decreased
12 Iodine	Normal ⁴⁰
13 Creatine	No data
14 Magnesium	Increased during relapse

D FUNCTION TESTS

1 Tolerance	
a Glucose	No data
b Glucose insulin	No data
c Insulin	No data
2 Adrenal water test	Positive in 2 cases ³⁹
3 Salt deprivation	No data
4 Balance	
a Nitrogen	Normal, if adequate protein intake negative right after parathyroidectomy ³⁹

E MISCELLANEOUS TESTS

1 Basal metabolic rate	Normal variations
2 Circulation time	No data
3 Sedimentation rate	No data
4 Specific dynamic action of protein	No data
5 Gastric analysis	Hyperacidity or achlorhydria
6 Electrocardiogram	Q-T interval may be shortened ^{60 62}
7 Fecal calcium	Varies with amount ingested in normals on low calcium diet fecal excretion is 75 per cent of total, in hyperparathyroid patients on a low calcium diet it is only 20 per cent of total on a high calcium diet (over 1 Gm) fecal excretions from 12 to 70 per cent of total (see Chart 83)

F URINARY HORMONE ASSAYS

1 FSH	No data probably normal
2 LH	
3 Estrogens	
4 Pregnanediol	
5 17 ketosteroids	
6 11 oxy steroids	
7 Aschheim Zondek	
8 TSH	

L GENITALIA

1 Male

- a Penis Normal
- b Testes Normal
- c Prostate Normal

2 Female

- a External Normal
- b Internal Normal

M NEUROMUSCULAR

1 Muscles

Hypotonus and decreased response to galvanic stimulation⁴⁸

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5 Paresthesias

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6 Reflexes

Normal

N SPEECH

Normal

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May be excessive in quantity (up to 12 l/24 hrs) and milky in appearance calcium phosphate casts especially with little or no albumin, calcium sand varying degrees of renal impairment pyuria and hematuria from pyelitis and/or pyelonephritis¹⁰

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k Iodine

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B HEMATOLOGY

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Normal or may be increased due to hemoconcentration

2 Hemoglobin

Normal or may be increased due to hemoconcentration anemia reported⁹

3 White blood cells

Normal

4 Differential

Normal

5 Coagulation time

Prolonged¹²³

6 Clot

Friable

IX ETIOLOGY

A UNKNOWN

B PARATHYROID

- 1 Adenoma
- 2 Hyperplasia
- 3 Carcinoma (very rare)
- 4 Indirect stimulus as
 - a Pregnancy
 - b Inadequate calcium intake¹⁶

C PARATHYROTROPIC HORMONE OF PITUITARY—Although existence of this hormone has not been established it may be a factor here if hypersecreted

X PATHOLOGY

A Gross

1 Parathyroids

- a Adenoma¹⁷ 88 66 63 53 61 104 105 73
111 146

(1) Incidence—86 per cent of cases of hyperparathyroidism

(2) Appearance

(a) Grayish brown as seen through capsule

(b) Cut surface — yellowish brown with red areas like splenic tissue

(c) The following may be found

- [1] Calcium deposits
- [2] Connective tissue septae
- [3] Hemorrhage
- [4] Necrosis
- [5] Infarction (rare)

(3) Remaining parathyroids

- (a) Normal or hypoplastic
- (b) Hyperplasia of chief cells has been noted at postmortem after removal of parathyroid adenoma¹¹⁷

(4) Location

	PER CENT
(a) Normal	90
(b) Aberrant	10
[1] Medias tinum	63 (approx)
[2] Thyroid	30
[3] Esophagus	7

(5) Weight

- (a) Mean—7 Gm
- (b) Maximum—120 Gm

(6) Volume—4 to 5 cc

(7) Number

- (a) Single—usually
- (b) Multiple—rarely

(8) Shape

- (a) Lobulated often
- (b) Irregular

(9) Function—a few adenomas are not hypersecretory

b Primary hyperplasia¹¹ 44 45 50 66
116 117 146

(1) Incidence—14 per cent of cases of hyperparathyroidism

(2) Appearance—deeper brown than adenomas

(3) All glands are involved, but not equally

(4) Size—4 cm x 3 cm x 3 cm

(5) Weight—up to 20 Gm each

(6) Volume—may reach 35 cc

(7) Shape—more irregular than adenoma

(8) Cysts and pseudopods—present

c Cancer¹⁷ 23 45 63 101 133

(1) Incidence

- (a) Very rare
- (b) Data in reported cases has sometimes been inconclusive

(2) Appearance

- (a) Cut surface—tannish gray to reddish brown
- (b) Nodules are attached to adjacent structures

(3) Location

- (a) Lower glands affected about five times as often
- (b) Aberrant tissue in
 - [1] Thyroid
 - [2] Thymus

(4) Size—may be 3 cm in diameter to masses measuring 11 cm x 11 cm x 4 cm

(5) Shape

- (a) Irregular nodules
- (b) Ovoid or round

(6) Number—single gland is involved in 90 per cent

(7) Consistency like that of normal liver

(8) Metastases late to

- (a) Surrounding tissues
- (b) Lymph nodes
- (c) Lungs

G BIOPSY

- 1 Endometrial
- 2 Testicular

H VAGINAL SMEAR

I SEMEN ANALYSIS

} No data, probably normal

VIII ROENTGENOGRAPHIC FINDINGS

A SKULL (see Figs 246 248)

- 1 Cranial vault

Osteoporosis, milary in type rarely osteofibroma or giant cell tumor without skeletal involvement¹⁷⁹

- 2 Sella turcica

Normal

- 3 Mandible

Ground glass appearance, cystlike cavities closely meshed trabeculae

- 4 Sinuses

Normal

- 5 Teeth

Loss of lamina dura,¹³³ diminished caries, epulides

- 6 Eyes

Corneal calcification may be seen⁶⁴

B EPIPHYSEAL STATUS (bone age)

May be retarded

C LONG BONES (femurs, radii and ulnae especially)^{53 57}

Normal in 55 per cent, the remainder show (see Fig 254)

- 1 Diffuse decalcification
- 2 Fibrous arrangement of trabeculae
- 3 Cysts, may be solitary
- 4 Fractures, but pseudofractures are unusual¹²⁰
- 5 Thinning of cortex
- 6 Medullary cavities which appear to be expanded

D VERTEBRAE

Osteoporosis mottling, compression, causing round back or kyphosis, scoliosis, often squashed or wedge shape or codfish type herniation of nucleus (see Figs 251 and 252)

E BONE TEXTURE

As above cancellous outline preserved in areas unaffected by cysts, fractures, etc

F MISCELLANEOUS

- 1 Chest (see Fig 250)

- a Deformity of ribs with marked loss of calcium
- b Intrathoracic adenoma may be seen directly or by visualization of the esophagus⁵⁷

- 2 Calculi may be

- a Small
- b Large
- c Unilateral
- d Bilateral
- e Multiple
- f Solitary
- g Ringed usually (calcium phosphate)
- h Renal
- i Vesical

- 3 Nephrocalcinosis^{10 11 141}

- a Calcification of renal parenchyma about the pyramids (tubules)
- b Diffuse involvement

- 4 Blood vessels—calcification may be noted

- 5 Metastatic calcification—more suggestive of secondary hyperparathyroidism associated with primary renal disease

- 6 Pelvis—changes as in long bones frequent site for bone cysts (see Fig 253)

- (3) Single or multiple cystic spaces
 - (4) Finely reticulated areas
 - d Long bones
 - (1) Greatest regeneration and repair at diaphyses
 - (2) Epiphyses show
 - (a) No change
 - (b) Decalcification only
 - 3 Kidneys
 - a Nephrocalcinosis
 - (1) Deposition of calcium within tubules
 - (2) Secondary nonspecific changes of severe disease
 - b Renal calculi²⁰
 - (1) Without infection
 - (a) Composition
 - [1] Calcium phosphate usually
 - [2] Calcium oxalate possibly
 - (b) Ratio is 2 or more parts of calcium to 1 part of phosphorus
 - (2) With infection and alkaline urine
 - (a) Composition
 - [1] Calcium phosphate
 - [2] Calcium oxalate
 - [3] Magnesium ammonium phosphate
 - (b) Ratio less than 2 parts of calcium to 1 part of phosphate
 - c Arteries
 - (1) Monckeberg type arteriosclerosis in long standing cases²
 - (2) Intimal calcification^{11a}
 - (3) Necrosis^{11b}
 - 4 Metastatic calcification of any tissue
- ## XI PATHOLOGIC PHYSIOLOGY
- ### A CHRONIC HYPERPARATHYROIDISM
- 1 Effects of excess parathyroid hormone
 - a Urinary excretion of the following is increased
 - (1) Water
 - (2) Nitrogen
 - (3) Calcium
 - (4) Phosphorus except with severe renal impairment
 - (5) Chloride
 - (6) Base
 - Serum
 - (1) Calcium—elevated
 - (2) Phosphorus—decreased
 - c Greater absorption of (see Chart 83)
 - (1) Calcium
 - (2) Phosphorus (probably)
 - 2 Hypercalcemia produces
 - a Decreased nerve or neuromuscular excitability of striated and smooth muscles
 - (1) Muscular
 - (a) Hypotonia²²
 - (b) Weakness
 - (2) Constipation
 - (3) Hearing impaired
 - (4) Electrocardiographic changes
 - b Calcium deposition in
 - (1) Conjunctivae
 - (2) Corneae
 - 3 Hypercalcinuria and phosphaturia and loss of other substances may result in
 - a Polyuria
 - b Urinary calcium phosphate sand
 - c Calcium deposits in renal tubules
 - d Stones
 - Osseous abnormalities (see below)
 - 4 Bone changes
 - a Calcium may be lost from the bones depending in part on
 - (1) Severity of disease (amount of hormonal secretion)
 - (2) Greater excretion than intake of calcium
 - (3) Unusual skeletal
 - (a) Stress
 - (b) Strain
 - b Tumors from collection of
 - (1) Osteoblasts
 - (2) Osteoclasts
 - (3) Marrow supporting tissue
 - c Cysts from
 - (1) Loss of calcium
 - (2) Fibrous replacement
 - d Anemia from
 - (1) Marrow changes if sufficiently severe
 - (2) Other causes
 - 5 Calculi formation is
 - a Due to an excess excretion of calcium which is precipitated in the renal pelvis
 - b Favored by
 - (1) Decreased fluid intake

- (d) Liver
- (e) Kidneys

(9) Hormonal inactivity in 50 per cent

2 Bones^{27 78 9}

- a Normal in some cases
- b Cysts
 - (1) Single
 - (2) Multilocular
- c Hemorrhages
 - (1) Recent
 - (2) Old
- d Evidence of marked bone resorption
 - (1) Bend easily
 - (2) Cut readily with a knife
- e Skull
 - (1) Bone resorption is slight
 - (2) Thickening of tables
- f Vertebrae may be collapsed
- g Order of involvement
 - (1) Vertebrae
 - (2) Sacrum
 - (3) Pelvis
 - (4) Skull
 - (5) Jaw
 - (6) Flat bones of thorax
 - (7) Short tubular bones of
 - (a) Hands
 - (b) Feet
- h Fractures and deformities are found

II MICROSCOPIC^{27 41 104 105 127}

1 Parathyroids

- a Adenoma (see Figs 255 and 256)
 - (1) Parenchyma
 - (a) Follicular structures are present
 - (b) Irregular blocks of epithelial (chief) cells
 - (c) Cystic areas
 - (2) Cellular changes
 - (a) Polyhedral types with distinct cell walls
 - (b) Pleomorphism is present
 - (c) Few mitoses which are not indications of malignancy
 - (d) Water clear cell type is found occasionally
 - (e) Oxyphil cell is unusual
 - (3) Actual malignancy is rare
- b Primary hyperplasia (or hypertrophy)^{11 117}
 - (1) Parenchyma
 - (a) Alveolar

- (b) Pseudoglandular
- (c) Compact
- (d) Cystic with hemorrhage

(2) Fatty tissue is absent

(3) Cells resemble normal water helle type

- (a) Cytoplasm absolutely water clear
- (b) Large and distended to 60 times their normal size (diameter 10 to 40 microns, nuclei 6 to 7 microns)

c Secondary hyperplasia

(1) Cells

- (a) Size—normal
- (b) All are involved
- (c) Higher glycogen content than in
 - [1] Hypertrophy
 - [2] Adenoma

(2) Fat tissue—scant

(3) Mitoses—absent

d Cancer^{33 43 61 62 100 133}

(1) Fibrous septa divide lobules in to irregular size and shape

(2) Stroma

- (a) Delicate fibrillar reticulum
- (b) Many capillary vessels
- (c) Blood and lymph vessel invasion by tumor cells

(3) Parenchyma

- (a) Closely packed cords or nests of cells
- (b) Follicles containing colloid may be found

(4) Cellular changes

- (a) All types found
- (b) Larger than normal usually
- (c) Mitotic figures are variable in number
- (d) Nucleoli are found

2 Bones (see Fig 258)

a Trabeculae are devoured by osteoclasts

b Connective tissue proliferation

c Marrow may show

(1) Fibrosis

(2) Giant cell tumors

- (a) Hyperactivity and accumulation of large multinucleated giant cells osteoclasts

(b) These are not malignant

B LABORATORY DATA

1 Borderline cases with equivocal blood findings

a Comment

(1) Urinary calcium excretion in normals may be doubled by injection of parathyroid extract without appreciable change in serum calcium level

(2) Low serum protein may mask elevation of serum calcium

(3) Renal failure may prevent usual decrease in serum phosphorus

(4) Ellsworth Howard test—failure to obtain increase in urinary excretion of phosphorus by injection of parathyroid extract may indicate

(a) Maximum response to in trinsic parathyroid hypersecretion

(b) Hyperparathyroidism providing renal function is adequate

b Quantitative urine calcium determination on 24 or 48 hr amounts

(1) Low calcium diet 4 to 7 days

(2) Patient should be ambulatory

(3) Values over 200 mg/24 hrs indicate an excess calcium excretion only but is evidence in favor of hyperparathyroidism

c Repeated serum (fasting) chemical analyses are significant if

(1) Calcium—above 10.5 mg %

(2) Phosphorus—below 3 mg %

(3) Alkaline phosphatase

(a) Normal if hyperparathyroidism is *not* associated with bone disease

(b) Increased

2 Early or mild cases

a Excess calcium in urine as shown by Sulkowitch test after 4 to 7 days on low calcium diet (no milk eggs or egg products)

b Calcium (serum)

(1) Normal

(2) Elevated slightly

c Phosphorus (serum)—lowered

d Alkaline phosphatase

(1) Normal

(2) Increased

3 Late cases

a Calcium (serum)—elevated

b Phosphorus (serum)—low, unless disease complicated by renal failure

c Alkaline phosphatase (serum)—high if bone changes are present or taking place

4 Spontaneous remissions are possible in all¹⁴

C ROENTGENOGRAPHIC FINDINGS

1 Normal in 55 per cent⁷

2 Generalized decalcification

3 Skull

a Smooth, ground glass

b Fuzzy appearance

4 Teeth—lamina dura may be

a Absent

b Disappearing

5 Kidneys—stones

6 Cystic lesions (see 38 \ A 2, B 2 \ A 4)

7 Bone tumors (see 38 \ A 2, B 2 \ A 4)

8 Fractures

9 Vertebral compression

D GENERAL

1 Adenoma may be demonstrated

a Palpable adenoma in 10 per cent

b Visualized intrathoracic adenoma (rare)

(1) Plain chest films

(2) Displacement of esophagus¹⁵

2 Bone deformities

XIV DIFFERENTIAL DIAGNOSIS

A OSTEOMALACIA (SECONDARY HYPERPARATHYROIDISM)¹⁷

1 Definitions

a Osteomalacia is a condition in which calcium salts fail to be deposited in normal and new osteoid tissue due to abnormal ratios in the level of calcium salts and inorganic phosphorus

b Rickets is osteomalacia occurring before epiphyseal closure and is identified by active proliferation of cartilage and other changes at the epiphyseal junction

2 Etiologic classification

a Hypovitaminosis D or avitaminosis D due to inadequate intake

- (2) Low urinary citrate level^{1 2}
 - (3) Urinary tract infections
 - (4) Repeated episodes of dehydration during any acute infection
 - Retarded by
 - (1) High fluid intake
 - (2) Decreased absorption of
 - (a) Calcium
 - (b) Phosphorus
 - (c) Vitamin D
 - (3) Low intake of
 - (a) Calcium
 - (b) Vitamin D
 - 6 Anorexia vomiting and secondary weight loss may be due to
 - a Hypercalcemia per se
 - b Other physiologic changes possibly
- B ACUTE HYPERPARATHYROIDISM**—Great excess of hormone causes in the following order^{1 9 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100}
- 1 Marked and increasing hypercalcemia (over 17 mg %)
 - 2 Polyuria
 - 3 Dehydration
 - 4 Calcium phosphate precipitation in
 - a Kidneys
 - b Other tissues
 - 5 Oliguria or anuria
 - 6 Renal failure
 - 7 Hemoconcentration
 - 8 Hyperphosphaturia
 - 9 Uremia
 - 10 Death⁷²
- 2 Gastro intestinal
 - a Polydipsia
 - b Mild abdominal discomfort
 - c Duodenal ulcer distress^{118 117}
 - d Dryness of throat
 - e Anorexia, especial distaste for milk and eggs
 - f Nausea
 - g Vomiting¹
 - h Weight loss
 - i Constipation
 - 3 Genito urinary
 - a Polyuria
 - b Renal colic
 - c Dysuria
 - d Nocturia
 - e Enuresis
 - f Hematuria
 - g Pyuria
 - 4 Bone changes
 - a Peripheral pain
 - b Backache, sudden onset usually
 - c Fractures
 - (1) Spontaneous
 - (2) Traumatic
 - d Shrinking of stature
 - (1) Scoliosis
 - (2) Kyphosis
 - (3) Compression of vertebrae
 - (4) Bowing of legs
 - e Pigeon breast
 - f Tumors of¹⁹
 - (1) Jaws
 - (2) Metacarpals
 - (3) Metatarsals
 - (4) Ends of long bones

XII SYMPTOMATOLOGY

A ACUTE HYPERPARATHYROIDISM

- 1 Restlessness
- 2 Tachycardia
- 3 Prostration
- 4 Coma
- 5 Dehydration
- 6 Acute renal failure
 - Urinary suppression
 - b Vomiting
 - c Headache

B CHRONIC HYPERPARATHYROIDISM

- 1 General vague complaints
 - a Fatigue
 - b Weakness
 - c Stiffness or aching of muscles
 - d Headache

XIII DIAGNOSIS

A COMMENT

- 1 Hyperparathyroidism will be diagnosed according to the imagination and vigil of the physician
- 2 It should be considered with the following (see 38 VII)
 - a Polydipsia
 - b Polyuria
 - c Renal stones
 - d Bone pain (including back)
 - e Spontaneous fractures
 - f Decreased height
 - g Unexplained
 - (1) Fatigue
 - (2) Vomiting
 - h Muscular hypotonia

- (3) Serum
- Calcium, phosphorus, phosphatase as listed above
 - The following are normal
 - Carbon dioxide combining power
 - Chlorides
 - Carotinoids
 - Vitamin A
 - Vitamin K
- (4) Fecal calcium relatively increased if intake is adequate
- (5) Bones
- Changes are dependent on duration and severity of the disease
 - Usual findings of rickets in childhood
 - Deminerlization of bone without loss of cancellous structure
 - Bending
 - Looser's zones (see 38 XIV A 5 e)
 - Excess production of osteoid tissue
 - Lamina dura may be absent
 - Expansion of rib cartilages
- b Osteomalacia or rickets—failure of vitamin D and calcium absorption due to steatorrhea (see Fig 259)
- General
 - Marked weakness
 - Emaciation
 - Gastro intestinal findings
 - An acidity may be present
 - Diarrhea may or may not occur
 - Tetany may be present with
 - Low serum calcium
 - Normal serum phosphorus
 - No renal stones
 - Urine
 - Titratable acidity—normal
 - Calcium—decreased
 - Ammonia—normal
 - Serum
 - Protein
 - Normal
 - Low
 - Cholesterol (plasma)—low
 - Calcium, phosphorus and potassium—low
 - Alkaline phosphatase—increased
 - Carbon dioxide combining power
 - Normal
 - Low
 - Lipase and diastase levels—may be altered
 - Carotenoids—decreased
 - The following are decreased
 - Vitamin A level
 - Vitamin K (prothrombin time)
 - Vitamin E as shown by therapeutic response
 - Feces
 - Calcium and phosphorus content are increased (non absorption)
 - Undigested meat fibers
 - High fat content
 - Bones
 - Normal
 - Decalcification or Looser's zones
- c Osteomalacia due to renal disease^{1 5 12 37}
- Tubular insufficiency without gross glomerular insufficiency (renal acidosis)
 - General
 - Nephrolithiasis or nephrocalcinosis may be present^{3 36}
 - Rickets and dwarfism in childhood
 - Potassium deficiency syndrome if not present may be precipitated by ammonium chloride administration³⁷
 - Theory of renal acidosis from tubular impairment and production of osteomalacia
 - Initial disorder
 - Defective tubular function (cause unknown)
 - Impairment of ammonia formation in tubules

- (1) Rickets
 - (a) Fetal
 - (b) Infant
 - (c) Childhood, up to usual time of epiphyseal closure
- (2) Adult osteomalacia
- b Hypovitaminosis D or avitaminosis D (and other vitamins) due to failure of absorption
 - (1) Idiopathic steatorrhea
 - (a) Celiac disease (children)
 - (b) Nontropical sprue (adults)
 - (2) Chronic pancreatitis
- c Hypovitaminosis D or avitaminosis D due to lack of response to ordinary amounts of this vitamin, without steatorrhea or kidney disease
- d Renal diseases
 - (1) Glomerular damage with or without tubular disease
 - (a) Renal rickets (infantilism up to usual time of epiphyseal closure)
 - (b) Osteomalacia and chronic nephritis
 - (2) Tubular disease only
 - (a) Renal acidosis due to
 - [1] Failure of ammonia formation
 - [2] Inability to secrete acid urine (conservation of base)
 - (b) Abnormal production of organic acids (Fanconi's syndrome)
- 3 Chemical classification as regards parathyroid response to calcium deficiency and as manifested by serum calcium phosphorus and phosphatase^{2 108}
 - a Normal parathyroid response
 - (1) Calcium—normal
 - (2) Phosphorus—decreased
 - (3) Alkaline phosphatase
 - (a) Normal—early before skeletal weakness stimulates the osteoblasts
 - (b) Increased—later after osteoblastic stimulation
 - b Normal parathyroid response which is ineffective because of paucity of available calcium
 - (1) Calcium—low
 - (2) Phosphorus—low
 - (3) Alkaline phosphatase—increased
 - c Absent or inadequate parathyroid response from defective or absent parathyroid tissue or, conceivably a lack of end organ response to hormone
 - (1) Calcium—low
 - (2) Phosphorus
 - (a) Normal
 - (b) Decreased (as in 3 b above)
 - (c) Increased — if glomerular failure
 - 4 Stages or degrees of osteomalacia based on normal parathyroid response (see 3 b above)
 - a Blood alterations without bone change
 - (1) Calcium—normal
 - (2) Phosphorus—low
 - (3) Alkaline phosphatase—normal
 - b Blood alterations with abnormal bone activity without roentgenographic evidence
 - (1) Calcium—normal
 - (2) Phosphorus—low
 - (3) Alkaline phosphatase—increased
 - c Blood alterations with bone changes, i.e., Looser's zones,^{93 100} but without generalized decalcification (Milkman's syndrome)
 - (1) Calcium—normal
 - (2) Phosphorus—low
 - (3) Alkaline phosphatase—increased
 - d Blood alterations with obvious and advanced osteomalacia (see 3 b above)
 - (1) Calcium—decreased
 - (2) Phosphorus—decreased
 - (3) Alkaline phosphatase—increased
 - 5 Clinical differentiation
 - a Osteomalacia or rickets—due to inadequate intake or utilization of vitamin D and calcium (as seen in the Orient)
 - (1) Tetany may be present when
 - (a) Calcium is low
 - (b) Phosphorus is
 - [1] Normal
 - [2] Decreased
 - (2) Urine
 - (a) Titratable acidity—normal
 - (b) Calcium
 - [1] Absent
 - [2] Decreased
 - (c) Ammonia—normal

- [c] Chlorides (may be low)
- [d] Carotenoids
- [e] Vitamin A
- [f] Vitamin K (pro thrombin time)
- (c) Bones as 5 c above
- (3) Osteomalacia or rickets due to glomerular failure with or without tubular disease
 - (a) General
 - [1] Hyperplastic parathyroid glands, may be 30 times normal size rarely do not respond¹²
 - [2] Disorder may be indistinguishable from late or treated hyperparathyroidism^{11,2}
 - [3] Tetany possible
 - [4] Signs of uremia
 - (b) Causes
 - [1] Glomerular nephritis
 - [2] Pyelonephritis
 - [3] Congenital^{10a}
 - [a] Hypoplasia
 - [b] Malformation
 - [c] Congenital dilatation of ureters
 - [4] Polycystic kidneys
 - (c) Urine
 - [1] Findings of chronic nephritis
 - [2] Calcium
 - [a] Normal
 - [b] Increased
 - [3] Phosphorus
 - [a] Normal
 - [b] Increased
 - [4] Potassium—increased
 - (d) Serum
 - [1] Nonprotein nitrogen (blood)—elevated
 - [2] Calcium—usually decreased
 - [3] Phosphorus—elevated
 - [4] Alkaline phosphatase—increased
 - [5] Carbon dioxide combining power—low
 - (e) Feces—no data
 - (f) Bones
 - [1] 'Renal' rickets in childhood
 - [2] Generalized demineralization due to increased bone destruction as opposed to lack of calcification of newly formed osteoid tissue
 - [3] Pseudocystic resorption occasionally
 - [4] Metastatic calcification sometimes
- d Osteomalacia from idiopathic calcinuria (rare) (see 38 \III B 1)¹³
 - (1) Urine
 - (a) Calcium—excessive
 - (b) Other findings—normal (compare with renal tubular disease)
 - (2) Serum
 - (a) Calcium
 - [1] Normal
 - [2] Decreased
 - (b) Phosphorus
 - [1] Normal
 - [2] Decreased
 - (c) Alkaline phosphatase—increased
 - (d) Other findings—normal
 - (3) Kidneys—pyelonephritis often
- e Milkman's syndrome¹⁴ 99 100
 - (1) Definition—a form of osteomalacia characterized by spontaneous pseudofractures (Looser's zones) without generalized skeletal decalcification
 - (2) Etiology as for any type of osteomalacia presented above, although apparently it most frequently occurs in
 - (a) Renal tubular insufficiency (see 38 \IV A 5 c)
 - (b) Steatorrhea
 - (3) Pseudofractures (as in osteomalacia with generalized decalcification)
 - (a) These may be
 - [1] Multiple
 - [2] Spontaneous

¹³ Albright et al believe the name should be retained even though it is osteomalacia, because of its characteristic radiologic appearance

- [c] Inability to secrete acid urine (i.e., to conserve base) which results in lowering of carbon dioxide and elevation of chlorides
 - [d] Calcium is a sparer of base for acid excretion and excessive in urine
- [2] Results
- [a] A low serum calcium stimulates parathyroid function
 - [b] Parathyroid hyperplasia in turn increases serum calcium to normal by causing hyperphosphaturia (excretion through glomeruli), hypophosphatemia and osteoblastic stimulation eventually
 - [c] If gastric acidity is low, absorption of calcium and phosphorus is decreased and may contribute to calcium deficiency⁶
- (c) Kidneys
- [1] Urine concentration (specific gravity)
 - [a] Normal
 - [b] Faulty
 - [2] Inulin clearance test—decreased
 - [3] Pyelonephritis may be present
- (d) Urine
- [1] Titratable acidity—low
 - [2] Sugar—occasionally
 - [3] Calcium—increased
 - [4] Ammonia—low
 - [5] Organic acids—normal
- (e) Serum (see above)
- [1] Sugar (blood)—may be low
 - [2] Potassium
 - [a] Normal
 - [b] Low
 - [3] Calcium—normal (rarely low)
 - [4] Phosphorus—low
 - [5] Alkaline phosphatase—elevated (usually)
 - [6] Chlorides—elevated
 - [7] Carbon dioxide combining power—low
 - [8] Carotenoids—normal
 - [9] Vitamin A level—normal
 - [10] Vitamin K (prothrombin time)—normal
- (f) Fecal calcium content may be as low as 20 per cent of urinary calcium
- (g) Bones
- [1] Normal
 - [2] Decalcification and/or Looser's zones
- (2) Osteomalacia and rickets due to Fanconi's syndrome (derangement of amino acid metabolism with hyperaminoaciduria)⁹⁰
- (a) Urine—increased excretion of
- [1] Titratable acidity
 - [2] Cellular contents
 - [3] Sugar
 - [4] Calcium
 - [5] Phosphorus
 - [6] Ammonia
 - [7] Acetone
 - [8] Amino acids
 - [9] Cystine (at times)
- (b) Serum
- [1] Calcium
 - [a] Normal
 - [b] Low
 - [2] Phosphorus—low
 - [3] Alkaline phosphatase—high
 - [4] Carbon dioxide combining power—low
 - [5] The following are normal
 - [a] Sugar (may be decreased)
 - [b] Nonprotein nitrogen (blood)

- b Serum
 - (1) Calcium—up to 18 or 20 mg %
 - (2) Phosphorus—low
- 3 Testosterone in treatment of carcinoma of breast
 - a Hypercalcemia symptoms usually absent
 - b Cause for effect is obscure
 - c Calcium (serum)—may reach 15 to 16 mg %
- 4 Estrogens—as for testosterone
- 5 Milk and alkali taken in excess over long periods of time⁴
 - a Conjunctivae
 - (1) Calcium deposits
 - (2) Band keratitis
 - b Renal function impaired
 - c Serum
 - (1) Calcium—increased
 - (2) Phosphorus
 - (a) Normal
 - (b) Increased
 - d Improvement on low calcium intake
- 6 Sudden bodily immobilization^{12 5 6 107}
 - a Occurrence
 - (1) Children or adolescents
 - (2) Paget's disease¹¹⁴
 - b Kidneys
 - (1) Calciumuria—excessive (1,300 mg /24 hrs)
 - (2) Temporary insufficiency
 - c Serum
 - (1) Calcium—increased about 15 mg %
 - (2) Phosphorus—normal
 - (3) Alkaline phosphatase—normal
 - d Bones show acute osteoporosis
- 7 Multiple myeloma (see below)
- 8 Malignant metastatic lesions (see below)
- 9 Boeck's sarcoid (see below)
- 10 Giant cell tumor may simulate epulis due to hyperparathyroidism
- 11 Miscellaneous causes
 - a Polycythemia vera
 - b Leukemia
 - c Pellagra
 - d Increased carbon dioxide content of blood
 - e Acute bone atrophy
 - f Advanced nephritis
- D RENAL CALCULI (idiopathic)
 - 1 Five to 15 per cent of idiopathic renal calculi are proven eventually to have hyperparathyroidism^{1 4 57}
- 2 Excess excretion of calcium without kidney disease except possibly in pyelonephritis¹¹
- 3 Serum
 - a Calcium
 - (1) Normal
 - (2) Decreased (slightly)
 - b Phosphorus—normal
- E CALCINOSIS
 - 1 Definition—abnormal deposit of calcium of unknown etiology in tissues⁴⁸
 - 2 Calcinosis universalis (see Fig 260)
 - a Palpable nodules of amorphous calcium involving
 - (1) Muscles
 - (2) Subcutaneous tissue
 - b Necrosis with draining sinuses may occur
 - 3 Dermatomyositis
 - a Tight skin similar to scleroderma
 - b Subcutaneous diffuse amorphous calcium deposits
 - 4 Metastatic calcinosis
 - a Hyperparathyroidism
 - b Hypervitaminosis D (see Protocol 38 XXVIII)
 - c Renal disease with secondary hyperparathyroidism
 - d Hypoparathyroidism
 - e Paget's disease
- F BONE DISEASES
 - 1 Multiple myeloma (rarely confused with hyperparathyroidism)
 - a Definition
 - (1) A primary malignant tumor of bone marrow characterized by areas of hyperplasia of plasma cells affecting the flat bones
 - (2) The disease is rapidly fatal although numerous exceptions occur in which the process is prolonged or apparently healed
 - b Urine
 - (1) Casts
 - (a) Calcium
 - (b) Phosphate
 - (2) Bence Jones protein in 50 to 70 per cent of cases^{1 11 17}
 - (3) Calcium may be increased
 - c Serum
 - (1) Protein—increased to 12 Gm %⁴

- [3] Uncalcified
- [4] Symmetrical, if not then they may be due to
 - [a] Trauma
 - [b] Other bone diseases, usually at site of bone pathology

- (b) Location
 - [1] Scapulae
 - [2] Glenoid cavities
 - [3] Ribs
 - [4] Necks of femur
 - [5] Pelvis

II CONDITIONS ASSOCIATED WITH DECREASED OR FAULTY FORMATION OF OSTEOID TISSUE

1 Osteoporosis^{8 117}

- a Definition—a disorder of tissue metabolism including decreased or faulty formation of osteoid tissue hence decreased total calcification
- b Etiology
 - (1) It may be associated with
 - (a) Acromegaly
 - (b) Cushing's syndrome
 - (c) Hyperthyroidism
 - (d) Eunuchoidism
 - (e) Menopause³²
 - (f) Diabetes mellitus (long standing and uncontrolled)

- (2) Malnutrition
- (3) Vitamin C deficiency
- (4) Disuse
- (5) Idiopathic

c Serum

- (1) Protein
 - (a) Normal
 - (b) Low
- (2) Calcium—normal
- (3) Phosphorus
 - (a) Normal
 - (b) Increased slightly⁹
- (4) Alkaline phosphatase—normal

d Bones

- (1) Normal in most cases except for calcium content
- (2) Cortex becomes thin eventually
- (3) Osteoid tissue decreases
- (4) Rare cases reported with osteitis fibrosa^{124 230}
- (5) Skull—normal usually
 - (a) Dental caries (in eunuchoids)
 - (b) Lamina dura persists

2 Osteogenesis imperfecta

- a Hereditocongenital disease
- b Serum
 - (1) Calcium—normal
 - (2) Phosphorus—normal
 - (3) Alkaline phosphatase—normal (unless associated with avitaminosis D)
- c Bones
 - (1) Osteoporosis
 - (2) Brittle
 - (3) Thin cortex
 - (4) Fractures are frequent
 - (5) Deformities, such as bowing of legs
 - (6) Lack phosphatase⁷⁴
 - (7) Skull
 - (a) Deformed
 - (b) Failure of closure of sutures
 - (c) Otosclerosis
 - (8) Cartilage—normal
- d General
 - (1) Short stature
 - (2) Scleras
 - (a) White
 - (b) Blue
 - (3) Poor dentition

C HYPERCALCEMIA

1 Hypervitaminosis D (see 103 VI for section on Vitamin D Fig 261)

- a Etiology—excessive dosage of vitamin D or A T 10 associated with normal or increased serum calcium, especially with renal impairment
- b Symptoms same as for hypercalcemia (see 38 VII)
- c Urine—increased output of
 - (1) Calcium
 - (2) Phosphorus (greater than calcium)

d Serum

- (1) Calcium
 - (a) Normal
 - (b) Increased
- (2) Phosphorus—increased
- (3) Alkaline phosphatase—increased

e Kidneys

- (1) Nephrocalcinosis
- (2) Renal insufficiency
- f Metastatic calcification

2 Parathyroid extract given in excess

- a All symptoms associated with hypercalcemia

- h Serum
 - (1) Calcium—up to 18 or 20 mg %
 - (2) Phosphorus—low
- 3 Testosterone in treatment of carcinoma of breast
 - a Hypercalcemia symptoms usually absent
 - b Cause for effect ■ obscure
 - c Calcium (serum)—may reach 15 to 16 mg %
- 4 Estrogens—as for testosterone
- 5 Milk and alkali taken in excess over long periods of time⁴
 - a Conjunctivae
 - (1) Calcium deposits
 - (2) Band keratitis
 - b Renal function impaired
 - c Serum
 - (1) Calcium—increased
 - (2) Phosphorus
 - (a) Normal
 - (b) Increased
 - d Improvement on low calcium intake
- 6 Sudden bodily immobilization^{12 75 8 107}
 - a Occurrence
 - (1) Children or adolescents
 - (2) Paget's disease¹¹⁴
 - b Kidneys
 - (1) Calcinuria—excessive (1,300 mg /24 hrs)
 - (2) Temporary insufficiency
 - Serum
 - (1) Calcium—increased about 15 mg %
 - (2) Phosphorus—normal
 - (3) Alkaline phosphatase—normal
 - d Bones show acute osteoporosis
- 7 Multiple myeloma (see below)
- 8 Malignant metastatic lesions (see below)
- 9 Boeck's sarcoid (see below)
- 10 Giant-cell tumor may simulate epulis due to hyperparathyroidism
- 11 Miscellaneous causes
 - a Polycythemia vera
 - b Leukemia
 - c Pellagra
 - d Increased carbon dioxide content of blood
 - e Acute bone atrophy
 - f Advanced nephritis
- D RENAL CALCULI (idiopathic)
 - 1 Five to 15 per cent of idiopathic renal calculi are proven eventually to have hyperparathyroidism^{1 4 67}
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 - (1) Casts
 - (a) Calcium
 - (b) Phosphate
 - (2) Bence Jones protein in 50 to 70 per cent of cases^{1 71 77}
 - (3) Calcium may be increased
 - c Serum
 - (1) Protein—increased to 12 Gm %³

- (2) Calcium
 - (a) Normal
 - (b) Increased (18 20 mg %)
 - 40 1-2
- (3) Phosphorus—may be low, if renal function adequate
- (4) Alkaline phosphatase^{119 140}
 - (a) Normal
 - (b) Increased slightly
- d Renal
 - (1) Nephrocalcinosis¹³⁹
 - (2) Calculi
 - (3) Insufficiency
- e Bones (see Fig 262)
 - (1) Generalized demineralization occasionally
 - (2) Punched out areas (see 38 XIV F 7)
- f Plasma cells in blood smear and sternal puncture reveals diagnosis
- 2 Malignant metastatic disease in bone²⁸
 - a Organs from which metastatic lesions frequently occur
 - (1) Thyroid
 - (2) Breasts
 - (3) Bronchi
 - (4) Kidneys
 - (5) Prostate (acid serum phosphatase elevated)
 - b Sites of metastases (usually well vascularized locations)
 - (1) Skull
 - (2) Ribs
 - (3) Sternum
 - (4) Vertebrae
 - (5) Proximal ends of
 - (a) Humeri
 - (b) Femurs
 - c Destructive lesions are common with or without general demineralization
 - d Bone biopsy is diagnostic
 - e Blood chemical analyses
 - (1) Normal
 - (2) Simulate primary hyperparathyroidism in all respects
 - f Primary tumor may be located
- 3 Osteitis deformans (Paget's disease)
 - a Definition—a bone disease of unknown etiology characterized in advanced cases by various deformities as
 - (1) Bowing of legs
 - (2) Skull enlargement
 - b Disease occurs at all ages
 - c Process may be asymptomatic
 - d Urine
 - (1) Calculi may form
 - (2) Calcium is not increased, except in sudden bodily immobilization because of fracture (see 99 V, 103 X)¹⁵⁴
 - (a) When osteoblastic activity is temporarily reduced
 - (b) Excess osteoclastic activity (always present) continues
 - e Serum
 - (1) Calcium
 - (a) Normal
 - (b) Increased
 - (2) Phosphorus—normal
 - (3) Alkaline phosphatase—to 150 Bu or more
 - f Bones
 - (1) Osteoblastic and osteoclastic activity are increased
 - (2) Size increased
 - (3) Trabeculations are coarse
 - (4) Skull (see Fig 263)
 - (a) Thick
 - (b) Moth eaten
 - (c) Lamina dura present
 - (5) Biopsy shows a mosaic appearance of cement lines (junction between new and old bone) within trabeculae which is pathognomonic⁶⁸
 - g Diagnosis is usually made by roentgenograms
- 4 Polyostotic fibrous dysplasia^{7 14 18, 65, 66 66 66 91 101}
 - a Synonyms
 - (1) Osteodystrophia fibrosa unilateralis
 - (2) Fibrous osteodystrophy
 - (3) Unilateral von Recklinghausen's disease
 - (4) Fibrous dysplasia
 - (5) Osteitis fibrosa disseminata
 - b It has been found in
 - (1) Gigantism
 - (2) Hyperthyroidism (rare)
 - (3) Sexual precocity in females (Albright's disease)^{16 67}
 - (4) Diabetes mellitus¹⁰⁹
 - c Skin
 - (1) Pigmented areas, irregular edges

- (2) Multiple cutaneous fibromas are absent
- d Serum
- (1) Cholesterol (plasma)—normal
 - (2) Calcium—normal
 - (3) Phosphorus
 - (a) Normal
 - (b) Low
 - (4) Alkaline phosphatase—may be increased with extensive involvement⁴⁹
- e Bones
- (1) Lesions regional in character
 - (2) Unilateral preponderance
 - (3) Unaffected areas are normal
 - (4) Sudden immobilization may cause same changes in serum calcium as in Paget's disease (see 38 XIV F 3)¹⁴⁴
 - (5) Pathologic fractures
 - (6) Lamina dura present
 - (7) Epiphyses and diaphyses may be affected
- 5 Neurofibromatosis (von Recklinghausen's disease—see Fig 265)^{7 139}
- a Onset—early in life
 - b Hypothalamic involvement
 - c Glioma of optic chiasm
 - d Skin⁷
 - (1) Multiple cutaneous neurofibromatosis (often familial)
 - (2) Areas of pigmentation with smooth edges
 - e Sexual precocity—rare in males
 - f Serum—the following are normal
 - (1) Cholesterol (plasma)
 - (2) Calcium
 - (3) Phosphorus
 - (4) Alkaline phosphatase
 - g Bones
 - (1) Lesions more symmetrical
 - (2) Tendency to involvement of
 - (a) Upper ends of tibiae
 - (b) Lower ends of femurs
 - (3) Less extensive damage than in polyostotic fibrous dysplasia
- 6 Boeck's sarcoid²³
- a Serum
 - (1) Protein—may be high
 - (2) Calcium—may be high
 - (3) Phosphorus—normal
 - (4) Alkaline phosphatase—may be high
 - b Bones
 - (1) Generalized decalcification absent
 - (2) Lamina dura present
 - (3) Small cystlike areas generally in
 - (a) Hands
 - (b) Feet
 - c Renal stones may be found
 - d Lung lesions are fairly typical
- 7 Eosinophilic granuloma
- a Serum—the following are normal
 - (1) Protein
 - (2) Calcium
 - (3) Phosphorus
 - (4) Alkaline phosphatase
 - b Bones
 - (1) Punched out areas of destruction occur in any part of the skeleton
 - (2) Lesions are radiosensitive
 - c Good prognosis
- 8 Osteosclerosis fragilis generalisata¹⁴⁰
- a Synonyms
 - (1) Osteopetrosis
 - (2) Marble bones
 - (3) Albers-Schonberg disease
 - (4) Osteitis condensans generalisata
 - (5) Osteoposthosis
 - b Disease does not resemble hyperparathyroidism
 - c Parathyroids may be enlarged occasionally⁴
 - d Alkaline phosphatase (serum)—slightly elevated
 - e Bones
 - (1) Extensive osteoid calcification
 - (2) Metastatic calcification
 - (3) Normal lamellar structure is absent
- 9 Other bone diseases should be considered but are unlikely to be mistaken for parathyroid disease if adequate studies are made
- a Tuberculosis
 - b Syphilis
 - c Tumors
 - d Cysts
- G LIPID DISEASES
- 1 Gaucher's disease¹³⁷
 - a Familial tendency³
 - b Occurrence
 - (1) Youth usually
 - (2) Adults occasionally

- c Physical status
 - (1) Patchy pigmentation of skin
 - (2) Fever
 - (3) Splenomegaly
 - (4) Hepatomegaly
 - d Blood count
 - (1) Normocytic normochromic anemia
 - (2) Leukopenia, relative lymphocytosis
 - (3) Thrombopenia with hemorrhagic tendency
 - e Serum chemical analyses
 - (1) The following are normal
 - (a) Cholesterol (plasma may be decreased)
 - (b) Calcium
 - (c) Phosphorus
 - (d) Alkaline phosphatase
 - (2) Bilirubin—increased
 - (3) Lipemia—absent
 - f Bones (see Fig 264)
 - (1) Osteoporosis
 - (2) Sclerosis
 - (3) Deformity especially
 - (a) Femurs
 - (b) Vertebrae
 - (4) Cotton wool appearance
 - (5) Spontaneous fractures
 - (6) Sternal puncture—typical Gaucher cells
- 2 **Niemann Pick's disease**¹³³
- a Familial tendency
 - b Congenital occurrence patient rarely lives beyond 2 years
 - c Physical status
 - (1) Evidence of cachexia
 - (2) Blue black discoloration of mucous membranes of mouth
 - (3) Skin pigmentation
 - (4) Splenomegaly
 - (5) Hepatomegaly
 - (6) Lymphadenopathy
 - d Blood count
 - (1) Normomacrocytic anemia
 - (2) Leukopenia
 - (3) Platelets
 - (a) Normal
 - (b) Decreased
 - e Serum chemical analyses are normal for
 - (1) Cholesterol (plasma may be increased slightly)
 - (2) Calcium
 - (3) Phosphorus
 - (4) Alkaline phosphatase
 - f Bones show slight osteoporosis
 - g 'Foam cells' in
 - (1) Blood
 - (2) Bone marrow
 - (3) Spleen
 - (4) Other tissues
- 3 **Lipoid granulomatosis (Hand Schuller Christian disease)**¹³⁴
- a Characteristics
 - (1) Exophthalmos
 - (2) Diabetes insipidus
 - (3) Xanthomata
 - (4) No external signs in some cases
 - b Serum
 - (1) The following are normal
 - (a) Calcium
 - (b) Phosphorus
 - (c) Alkaline phosphatase
 - (2) Cholesterol (plasma)
 - (a) Normal
 - (b) Increased
 - c Bones
 - (1) Destructive areas may be found
 - (2) Punched out lesions
 - (3) Uninvolved bone is normal in texture
 - (4) Old sites may appear cystic due to fibrosis
 - (5) Spontaneous fractures
 - (6) Biopsy of fresh areas show foam cells containing cholesterol
 - (7) Lesions are radiosensitive
- XV COMPLICATIONS SEQUELAE AND ASSOCIATED DISEASES**
- A **SEQUELAE** (these include all signs or symptoms related to bone or renal changes—see 38 VI, XIV)
- 1 Pyelitis
 - 2 Pyelonephritis
 - 3 Renal failure²³
 - 4 Tetany, from infarction of adenoma
 - 5 Compression of spinal cord as a result of fracture or collapse of vertebrae
 - 6 Acute hyperparathyroidism
 - 7 Arterial disease¹³⁵
 - 8 Metastasis⁶⁷
- B **ASSOCIATED DISEASES**
- 1 Acromegaly³²
 - 2 Hyperthyroidism

- 3 Myxedema⁸⁴
- 4 Paget's disease
- 5 Duodenal ulcer^{116 117}
- 6 Aritaminosis D

XVI TREATMENT

A MEDICAL

- i Indications—high serum calcium level (17 mg % or over) to lessen impending danger of²³
 - a Renal failure
 - b Excessive hypercalcemia before surgery

2 Therapy

- a High fluid intake, including intra venous saline
- b Low calcium (below 0.25 Gm a day) and phosphorus diet

- 3 Results—management should be helpful temporarily

B ROENTGEN

1 Indications—if

- a Surgery is
 - (1) Refused
 - (2) Contraindicated
- b At operation
 - (1) Part of adenoma is not removed
 - (2) Tumor is not found

2 Results

- a Isolated cases may respond favorably
- b Generally disappointing⁷

C SURGICAL (see Figs 266 and 267)

1 Indications—to

- a Prevent kidney damage
- b Avoid further bone involvement
- c Relieve symptoms

2 Comment

- a Adequate knowledge of parathyroid embryology is helpful¹⁰⁴
- b Special skill is required in this field^{50 87 95}
- c Size of adenoma or parathyroid hypertrophy may roughly parallel severity of disease
 - (1) If small adenoma (1 to 2 cm) is found in an advanced case a larger one must be sought
 - (2) All adenomas should be removed (see 34 \)
 - (3) Finding of one normal gland
 - (a) Hypertrophy of the other parathyroids excluded

- (b) Adenoma is therefore present, if the diagnosis is correct

- (4) Subtotal resection of all hypertrophic glands is necessary (see 38 \)

- (5) Normal glands should not be removed

- d High serum phosphatase is considered an indication, by some for removal of parathyroid pathology in stages to avert severe postoperative tetany (see 38 \VI C 5)⁷⁷

- e With renal damage, less radical resection is required because parathyroid secretion is necessary to compensate for

- (1) Rise in serum phosphate
- (2) Depression of serum calcium

- f Removal of carcinoma follows the surgical principles for any malignant process

3 Operation for parathyroid adenoma

a Anesthesia

- (1) General
- (2) Nitrous oxide ether
- (3) Cyclopropane

b Exploration of neck^{1 35}

- (1) Wide collar incision
- (2) Platysma elevated with skin flaps
- (3) Sternomastoid dissected free of sternothyroid and omohyoid opposite cricoid cartilage sufficiently to see ansa hypoglossal nerve
- (4) Sternothyroid muscles divided in midline from thyroid cartilage to manubrium
- (5) Prethyroid muscles are cut transversely
- (6) Contour of thyroid inspected for tumor mass
- (7) If none is found lobe is freed with complete lateral exposure
- (8) Inferior thyroid artery and recurrent nerve are located
- (9) Inspect for superior glands from inferior thyroid artery to upper pole and above
- (10) Parathyroids may lie on lateral anteroposterior or medial surface of thyroid

- (11) Check lower poles of thyroid, following small arterial branches from inferior thyroid artery
- (12) If no glands are found, a wider dissection is performed from upper lobe to larynx
- (13) Areolar tissue as far lateral as carotid sheath is inspected also
- (14) Examine behind esophagus, although absence of vascular pedicle probably excludes presence of gland or tumor
- (15) Carry dissection down into posterior mediastinum on either side
- (16) Identify thoracic duct on left
- (17) Inspect anterior mediastinum as far as direct vision is possible
- (18) Identification of vascular pedicles may give immediate clue to location of adenoma
- (19) Thymic rests may enclose para-thyroid tissue, inspect before removal
- (20) Resection of whole thyroid is rarely necessary, adenoma may be palpated within thyroid
- c Exploration of mediastinum¹
 - (1) Incise skin to third interspace
 - (2) Insert finger posterior to manubrium and blunt dissect space for cutting sternum
 - (3) Opening is made on one side at third interspace and pleura pushed away
 - (4) Tunnel behind manubrium to third interspace
 - (5) Sternum is cut by Lebsche knife
 - (6) Anterior mediastinum is explored on that side if no tumor other side is examined in the same way
 - (7) Search from neck down to right auricle
 - (8) The tumor may be found
 - (a) On either side of aorta in the middle of mediastinum
 - (b) Anterior or posterior to innominate vein
 - (c) Within thymus
 - (9) Suture sternum with stainless steel wire
- (10) Close without drain after all air and fluid removed from mediastinum by suction
- 4 Results (see Chart 84)
 - a Serum
 - (1) Calcium falls to normal within a few days
 - (2) Phosphorus rises
 - b Improvement in general well being including correction of symptoms
 - c Recalcification of bone
 - (1) Exact percentage is unknown
 - (2) Snapper reports only 70 per cent were recalcified 10 years after operation (postmortem analyses)^{2,3}
 - (3) Many show little evidence of this, because of other factors, as menopause, senility, etc
 - d Failure to find adenoma may require a subsequent operation
- 5 Postoperative complications
 - a Tetany
 - (1) General
 - (a) Occurs in 50 per cent of cases
 - (b) More likely with
 - [1] High preoperative alkaline serum phosphatase (above 20 Bu)
 - [2] Marked bone decalcification
 - (c) Severe and difficult to manage sometimes because
 - [1] Osteoblastic activity is increased
 - [2] Osteoclastic process ceases with removal of excess parathyroid secretion
 - [3] Bones will readily absorb all the available calcium or will not yield it to blood stream, due to surrounding osteoblasts⁴
 - (2) Serum
 - (a) Calcium falls quickly
 - (b) Phosphorus may decrease even when tetany is present as from osteomalacia
 - (c) Alkaline phosphatase may rise after operation

- (d) Later concentrations return to normal
 - (3) Treatment
 - (a) When symptoms are very mild, withholding therapy may speed up function of remaining glands and hasten recovery from hypocalcemia
 - (b) If the tetany is moderately severe, usual measures may be employed (see 38 \\\I)
 - (c) For severe cases constant intravenous administration of calcium may be necessary
 - b Oliguria
 - (1) Occurrence—frequent
 - (2) Nonprotein nitrogen—rises temporarily
 - (3) Treatment—hypertonic glucose and saline intravenously
 - c Acidosis⁸
 - (1) Serum
 - (a) Sodium—decreased
 - (b) Chlorides—increased
 - (c) Carbon dioxide combining power—decreased
 - (2) Treatment
 - (a) Sodium bicarbonate orally
 - (b) Sodium lactate intravenously
 - d Transient difficulty in focusing eyes
 - e Mental changes
 - (1) Acute psychosis
 - (2) Depression
 - (3) Treatment—may subside with management of tetany
 - f Paralytic ileus—a rare complication
- XVII PROGNOSIS**
- A ACUTE HYPERPARATHYROIDISM—Disease may be rapidly fatal unless recognized early
 - B CHRONIC HYPERPARATHYROIDISM
 - I Without surgical procedure
 - a Actual morbidity is not known
 - b Average duration of disease is 5 to 7 years
 - Dependent on severity of hypersecretion
 - (1) Mild degree of hyperactivity with adequate vitamin D and calcium intake might be compatible with average outlook
 - (?) Very active disease indicates unfavorable prognosis
 - d Spontaneous remissions or cures are possible but probably rare⁹
 - e Pregnancy^{66 111 131}
 - (1) Normal
 - (2) Stillborn
 - (3) Infantile tetany
 - 2 Postoperative outcome
 - a Renal changes
 - (1) If kidney function is adequate improvement after surgery should be very favorable
 - (2) Nephrocalcinosis is not reversible except possibly in early cases
 - (3) Azotemia may persist in some cases (see Chart 85)
 - (4) Progressive tubular impairment may cause
 - (a) Acidosis
 - (b) Failure of recalcification
 - b Bones
 - (1) Relief of pain
 - (2) Recalcification by calcium retention, occasionally this may not occur, due to lack of increased osteoblastic activity¹⁴
 - (3) Recovery may be retarded because of
 - (a) Menopause
 - (b) Senility
 - (c) Chronic infection
 - (d) Inanition
 - (e) Vitamin D deficiency¹⁻³
 - (f) Other diseases complicating picture
 - c Pregnant patient—mother and child normal¹¹¹
 - 3 Recurrence after surgery
 - a Unlikely after removal of adenoma
 - b Possible recurrence with
 - (1) Hyperplasia
 - (2) Malignancy^{18 43 "}
 - (3) Insufficient removal
 - c Several years or more may be necessary to demonstrate recalcification by roentgenographic films
- XVIII CAUSES OF DEATH**
- A ACUTE HYPERPARATHYROIDISM
 - B RENAL FAILURE
 - C INTERCURRENT INFECTION
 - D INCIDENTAL DISEASES

TABLE 46 TABULATION OF URINARY FECAL AND SERUM CALCIUM AND PHOSPHORUS UNDER VARIOUS CONDITIONS [622]

[illegible]

CONDITIONS	GASTRO										[623]					
	PRIMARY		BALANCE		INTESTINAL ABSORPTION		UTILIZATION		FECAL			SECRET				
	Calcium	Phosphorus	Calcium	Phosphorus	Nitrogen	Calcium	Phosphorus	Utilization of calcium—amobolism	Rejection or loss of calcium	Calcium	Phosphorus	Calcium	Phosphorus	Phosphatase	Carbon dioxide combining power	Chlorides
Sprue or steatorrhea	+	+	1	1	1	1	1	1	1	+	+	1	1	+	1	N
Negative nitrogen balance infections or immobilization	+	+	1	1	1	1	1	1	1	+	+	1	1	+	1	N
Hypoparathyroidism	4+	4+	1	1	1	1	1	1	1	+	+	1	1	+	1	N
Hypoparathyroidism	+	+	1	1	1	1	1	1	1	+	+	1	1	+	1	N
Hypothyroidism	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	N
Hypothyroidism	+	+	1	1	1	1	1	1	1	+	+	+	+	+	+	N
Hypoadrenocorticalism	+	+	1	1	1	1	1	1	1	+	+	+	+	+	+	N
Hypogonadism	N	N	1	1	1	1	1	1	1	+	+	+	+	+	+	N
All signs are relative amounts																
0 = Absent																
- = Less than normal																
N = Normal																
+ = Increased																
4+ = Excess																
? = Questionable or unknown																
V = Normal increased or decreased																

HYPERPARATHYROIDISM⁶⁰

PROTOCOL XXVIII Fig 261

Secondary Hyperparathyroidism with Calcinosis, Probably Due to
Renal Disease and Excess Ingestion of Vitamin D

Family history Tuberculosis

Past medical Patient well until 5 years ago

Chief complaints Pain in the legs and right shoulder for 7 months

History of present illness

YEARS

5 Frontal headaches, anorexia, weakness, thirst, nocturia and urgency
Albuminuria

4½ Edema of ankles in the evening and puffiness around the eyes in the morning

1 Drank 1 to 2 milk shakes daily, and later 1 to 2 quarts of milk daily
Vitamin D taken in large doses for 1 year

MONTHS

8 Severe diarrhea for 6 weeks with a weight loss of 15 lbs

7 Several large lumps, 6 to 8 in in diameter, appeared on his shoulders, left arm and both thighs A few months later a mass developed in right axilla

5 Dyspnea and severe pain with exertion in thighs hips and sacrum
Biopsy of one of the masses showed calcinosis

Physical examination Age 33, male, single

Extreme pallor, evidence of weight loss uremic breath, but alert Weight 121¾ lbs Height 64¾ in Pulse 90 BP 144/94 Skin coarse and dry Buccal mucosa, palms and nail beds pale Cauliflower shaped tender resilient 5 x 6 in to 6 x 8 in masses, apparently present in the muscle over the deltoids, tensor fasciae latae right trapezius crest and right axilla Liver palpable at costal margin and tender Right testis was small, soft and tender Prostate gland enlarged to twice the normal size and felt boggy Optic disks arteriosclerosis, Grade II Radial vessels rigid and beaded Reflexes hyperactive Chvostek's sign positive on left

Laboratory data Urine—specific gravity 1.015, albumin 2 plus, sediment 20 to 40 WBC, Sulkowitch test negative, culture hemolytic staphylococcus aureus RBC 2,990,000 Hgb 9.6 Gm WBC 9,750

Differential polymorphonuclears 85.0%, band forms 0.5%, lymphocytes 11.0%, monocytes 1.5%, eosinophils 3.0% Hematocrit 28% NPN 113, 102, 115 and 129 mg % Total protein 9.0 Gm %, albumin 4.5 Gm %, globulin 4.5 Gm %, A/G ratio 1.1 Plasma cholesterol 115 mg % Serum calcium 11.1 mg % Serum phosphorus 8.8 mg % Serum phosphatase alkaline 6 B u, acid 0.3 units (normal) Serum chlorides 561 mg % Carbon dioxide combining power 21 volumes % Water test positive Sedimentation rate 115 mm/hr Bromsulphalein 5% dye retention in 1 hr Cephalin flocculation negative Urea clearance 8% of normal Calcium balance studies diet 0.099 to 0.1 Gm of calcium daily for 5 days urine calcium was low in view of the marked renal impairment

Roentgenographic findings Skull—osteoporotic changes consistent with hyperparathyroidism Shoulders and hips—masses of calcification in soft tissues surrounding, but not involving the hip and shoulder joints Marked calcification of arteries in both shoulder areas, throughout the pelvis, aortic knob, hands and abdomen Long bones normal. Pyelogram I V—no excretion on either side in 1½ hrs retrograde—kidneys were small, and their outlines well visualized, the pelvis and calices of both were normal with good cortical margins bilaterally Esophagus normal, with no evidence of a mediastinal mass on fluoroscopic examination

Treatment Blood transfusion 500 cc Low phosphorus diet with protein 70 Gm a day Amphojel 2 teaspoonfuls before and after meals and at bedtime Three liters of fluid daily, including 1 pint of milk

Progress Patient stated at a later date that metastatic calcifications were disappearing but eventually he died

Comment A case of marked renal impairment and associated metastatic calcinosis resulting from altered phosphorus and calcium metabolism The excessive intake of vitamin D may have been a factor in the renal insufficiency Metastatic calcifications have been reported in cases of vitamin D toxicity

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FIG 245 HYPERPARATHYROIDISM (See also Figs 246 251 254 and 255) Age 61 Hyperparathyroidism due to substernal parathyroid adenoma. Picture taken 6 months after removal of adenoma. Note dorsal round back and chest deformity (Lahey F H and Haggart G E Hyperparathyroidism clinical diagnosis and operative technique of parathyroidectomy Surg Gynec & Obst 60 1033 1051)



FIG 246 HYPERPARATHYROIDISM (See also Figs 245 251 254 and 255) Skull in hyperparathyroidism. Note thickening of both tables of the skull and the fuzzy appearance indicating marked osteoblastic activity (Lahey F H and Haggart G E Hyperparathyroidism clinical diagnosis and operative technique of parathyroidectomy Surg Gynec & Obst 60 1033 1051)



FIG 247 SKULL IN HYPERPARATHYROIDISM. Note thinning of tables at top of skull and mottled appearance

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FIG 247 SKULL IN HYPERPARATHYROIDISM. Note thinning of tables at top of skull and mottled appearance

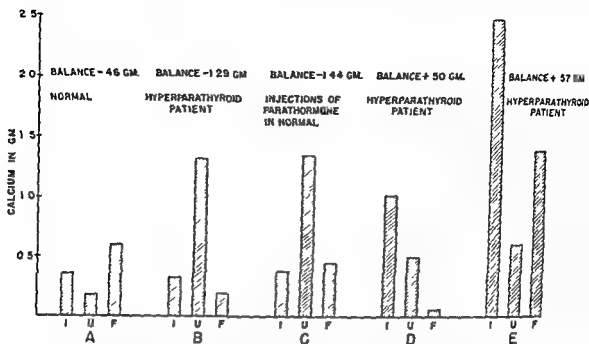


CHART 83 CALCIUM BALANCES IN THE NORMAL PERSON THE NORMAL TREATED WITH PARATHYROID EXTRACT AND HYPERPARATHYROIDISM (I = intake U = urinary calcium F = fecal calcium) (A) Normal human on low calcium intake (0.3 Gm) showing relationship between urinary and fecal excretion. Note that there is a negative balance the body drawing on its reserves for calcium. (B) Hyperparathyroidism on 0.3 Gm of calcium daily. Observe the greater negative calcium balance. Urinary output is increased and better absorption may have taken place in the gastro intestinal tract. (C) Induced hyperparathyroidism in a normal person by injection of parathyroid extract. Note similarity to (B). (D) Hyperparathyroidism on an essentially normal calcium intake. Note that calcium loss is avoided when adequate intake is supplied in this experiment. (E) Hyperparathyroidism on large calcium intake. Note that urinary output of calcium is not increased and that greater amounts of calcium are unabsorbed. It would appear in this case that maximum absorption had occurred. Contrast with calcium output in tetany on large intake of calcium (Bauer W Albright F and Aub J C Studies of calcium and phosphorus metabolism II The calcium excretion of normal individuals on a low calcium diet including data on a case of pregnancy J Clin Investigation 7 75 96 Albright F Bauer W Ropes M and Aub J C Studies of calcium and phosphorus metabolism IV The effects of the parathyroid hormone J Clin Investigation 7 139 181 Bauer E Albright F and Aub J C A case of osteitis fibrosa cystica (osteomalacia?) with evidence of hyperactivity of the parathyroid bodies Metabolic study II J Clin Investigation 8 229 258)

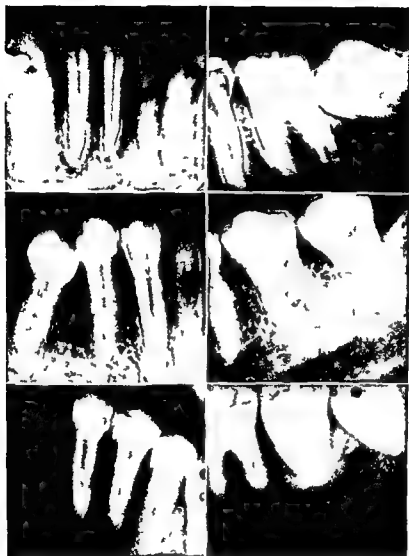


FIG 248 LAMINA DURA The disappearance of this structure occurs in hyperparathyroidism (primary or secondary) with generalized skeletal decalcification. It is not pathognomonic of hyperparathyroidism since it may occur occasionally in osteoporosis and possibly with extensive periodontal infection. The presence of the lamina dura does not exclude hyperparathyroidism (*Top left and right*) Normal lamina dura (periodontal membrane) is demonstrated very well (*Middle left and right*) Partial loss of lamina dura in a case of hyperparathyroidism (*Bottom left and right*) Complete loss of lamina dura in case of hyperparathyroidism



FIG 249 SKULL IN HYPERPARATHYROIDISM. Note cystic area (epulis) in left mandible (verified case). These are often noted in dental films as the first evidence of the disease.



FIG 250 CHEST IN HYPERPARATHYROIDISM (See Figs 245, 246, 251 and 255). Note sagging ribs. The rounded shadow in the hilum proved to be the adenoma.



FIG 251 DORSAL SPINE IN HYPERPARATHYROIDISM (See also Figs 245, 246, 250 and 255). Note decalcification and wedging of vertebrae. The codfish vertebrae i.e. the concavity produced by expansion intervertebral of nucleus pulposus against softened vertebrae is well shown (Lacey F H and Haggart G E. Hyperparathyroidism: clinical diagnosis and operative technique of parathyroidectomy. Surg. Gynec. & Obst. 60: 1033-1051).



FIG 252 DORSAL SPINE IN HYPERPARATHYROIDISM Note almost complete compression of one dorsal vertebra (A) and herniation of nucleus pulposus (B) (verified case)



FIG 253 PELVIS IN HYPERPARATHYROIDISM Cystic areas are numerous in both iliac as well as in other parts (verified case)



FIG 254 HYPERPARATHYROIDISM Tibia and fibula in advanced hyperparathyroidism Note marked deformity, cystic areas involving most of the bone Parathyroid tumor found within lobe of thyroid gland



FIG 249 SKULL IN HYPERPARATHYROIDISM Note cystic area (epulis) in left mandible (verified case) These are often noted in dental films as the first evidence of the disease



FIG 250 CHEST IN HYPERPARATHYROIDISM (See Figs 245 246 251 and 255) Note sagging ribs The rounded shadow in the hilum proved to be the adenoma



FIG 251 DORSAL SPINE IN HYPERPARATHYROIDISM (See also Figs 245 246 250 and 255) Note decalcification and wedging of vertebrae The codfish vertebrae i.e. the concavity produced by expansion intervertebral of nucleus pulposus against softened vertebrae is well shown (Labeys F H and Haggart G E Hyperparathyroidism clinical diagnosis and operative technique of parathyroidectomy Surg Gynec & Obst 60 1033 1051)

FIG 258 FIBROCYTIC OSTEITIS The cellular bone marrow is completely replaced by fibrous tissue. The remnants of the bone trabeculae are surrounded by islands of multinuclear osteoclasts. After removal of parathyroid adenomas the latter are quickly replaced by osteoblasts (Snapper I Medical Clinics on Bone Diseases New York Interscience p 22)



FIG 259 OSTEOMALACIA ASSOCIATED WITH RHEUMATOID ARTHRITIS POOR CALCIUM ABSORPTION AND CARCINOMA OF PANCREAS

Chief complaint Muscle weakness for 4 years

History of present illness Always well. No dietary deficiencies. Pain in knees and ankles noted for 3 years. Exploratory abdominal operation performed elsewhere was negative. Long convalescence. Tetany attacks began 3 years previously. One year before admission struck by a truck and fractured his pelvis. Nocturnal

Physical examination Age 36 male. Weight 100 lbs. Height 61½ in. BP 85/60. Pulse 104. Asthenic chronically ill man requiring crutches to walk. Pitting edema of ankles and local heat. Slight dorsal kyphosis. Chvostek's and Trousseau's signs positive.

Laboratory data Urine: albumin trace; sugar negative; specific gravity 1.021; reaction alkaline; sediment 1 to 3 WBC. Sulkowitch test negative. RBC 4,260,000. Hgb 89 Gm. WBC 5,500. Differential normal. Hinton negative. NPN 18 mg. Total serum protein 5.9 to 6.4 Gm. albumin 3.2 Gm. and globulin 3.2 Gm. Serum calcium 6.6 and 8 mg. Serum phosphorus 12 and 11 mg. Serum sodium 140 mEq/l. Serum potassium 19.5 mg. Serum amylase 119 units. Sedimentation rate 35 mm in 1 hr. Intravenous injection of 20 cc calcium gluconate before injection serum calcium—8 mg. 10 min after 8 mg. 40 min after 7 to 8 mg. 60 min after 7.2 mg.

Röntgenographic findings Skull—thin vault with marked calcium loss and definite platybasia (from soft bones). Lamina dura barely visible. Ankles and

feet—marked decalcification and edema of tissues. Transverse fracture of tibia.

Comment Patient died elsewhere before therapy was initiated. Postmortem revealed carcinoma of pancreas. Parathyroids were not identified, eliminating in all probability parathyroid hyperplasia.





FIG 255 PARATHYROID ADENOMA (See also Figs 245 246 251 and 254) The dark est staining cells are oxyphils The medium staining cells are the chief cells Those with clear cytoplasm are the wasserhelle cells



FIG 257 NORMAL BONE Microphoto graph of normal bone with concentric bone layers The bone marrow is cellular and does not contain fibrous tissue (Snapper I Medical Clinics on Bone Diseases New York Interscience p 22)

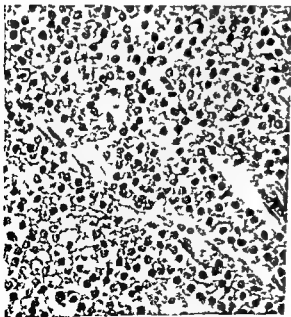


FIG 256 PARATHYROID ADENOMA Wasserhelle cell parathyroid adenoma Note the water clear cytoplasm which distinguishes this type of parathyroid adenoma (x 310)

FIG. 258 FIBROCYSTIC OSTEITIS The cellular bone marrow is completely replaced by fibrous tissue. The remnants of the bone trabeculae are surrounded by islands of multinuclear osteoclasts. After removal of parathyroid adenomas the latter are quickly replaced by osteoblasts (Snapper I. Medical Clinics on Bone Diseases New York Interscience p. 22)



FIG. 259 OSTEOMALACIA ASSOCIATED WITH RHEUMATOID ARTHRITIS POOR CALCIUM ABSORPTION AND CARCINOMA OF PANCREAS

Chief complaint Muscle weakness for 4 years

History of present illness Always well. No dietary deficiencies. Pain in knees and ankles noted for 3 years. Exploratory abdominal operation performed elsewhere was negative. Long convalescence. Tetany attacks began 3 years previously. One year before admission struck by a truck and fractured his pelvis. Nocturia.

Physical examination Age 36 male. Weight 100 lbs. Height 61½ in. BP 85/60. Pulse 104. Asthenic, chronically ill man requiring crutches to walk. Pitting edema of ankles and local heat. Slight dorsal kyphosis. Chvostek's and Trousseau's signs positive.

Laboratory data Urine: albumin trace, sugar negative, specific gravity 1.021, reaction alkaline, sediment 1 to 3 WBC. Sulkowitch test negative. RBC 4,260,000. Hgb 89 Gm. % WBC 5,000. Differential normal. Hinton negative. NPN 18 mg. % Total serum protein 5.9 to 6.4 Gm. % albumin 3.2 Gm. % and globulin 3.2 Gm. % Serum calcium 6.6 and 8 mg. % Serum phosphorus 1.2 and 1.1 mg. % Serum sodium 140 mEq/l. Serum potassium 19.5 mg. % Serum amylase 119 units. Sedimentation rate 35 mm in 1 hr. Intravenous injection of 20 cc calcium gluconate before injection serum calcium—8 mg. % 10 min after 8 mg. % 40 min after 10 to 8 mg. % 60 min after 12 mg. %

Roentgenographic findings Skull—thin vault with marked calcium loss and definite platybasia (from soft bones). Lamina dura barely visible. Ankles and

feet—marked decalcification and edema of tissues. Transverse fracture of tibia. *Comment* Patient died elsewhere before therapy was initiated. Postmortem revealed carcinoma of pancreas. Parathyroids were not identified, eliminating in all probability parathyroid hyperplasia.





FIG 260 CALCINOSIS UNIVERSALIS IN A CHILD OF THREE Multiple nodules developed under the skin at the age of 1 occasionally requiring incision because of fluctuation. All calcium deposits were amorphous. Laboratory studies were normal: Urine calcium 97 mg/24 hrs, NPN 19 mg %, Serum calcium 9.4 and 10.0 mg %, Serum phosphorus 4.5 and 5.1 mg %, Serum alkaline phosphatase 4.5 IU. Blood chlorides 98 mEq/l, Carbon dioxide combining power 24 mEq/l. No treatment known.



FIG 261 METASTATIC CALCINOSIS (See also Protocol 38 \VIII). The condition was associated with renal insufficiency and may have been caused or aggravated by excess vitamin D intake (see 38 \IV C 1). (Bottom) Note also marked arterial calcification (arrows) (Kaufman M and Dow J W. Hyperparathyroidism with calcinosis probably secondary to renal disease. *Lahey Clin Bull* 5:21-26).



FIG 262 MULTIPLE MYELOMA OF THE SKULL



FIG 263 PAGET'S DISEASE Age 41 male No symptoms other than occasional spells of vertigo and slight impairment of hearing Serum alkaline phosphatase is increased in these cases with normal serum calcium and phosphorus Osteolytic phase pre-ent



FIG 64 POLYOSTOTIC FIBROUS DYSPLASIA Age 25 male Uninvolved bone is normal in appearance No abnormal findings in blood or urine

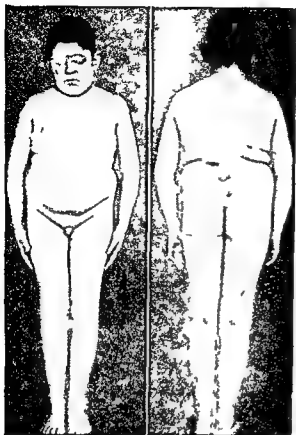


FIG 265 NEUROFIBROMATOSIS WITH TYPICAL CAFÉ AU LAIT PIGMENTATION (SMOOTH EDGED) BONE CHANGES AND PITUITARY DWARFISM

Family history Mother and sister have similar pigmentation and evidence of neurofibromatosis

Past medical First abnormality observed was cryptorchidism for which an unsuccessful operation was performed at 16 years Retarded mental and physical development (IQ—59)

Physical examination Age 18 Weight 102 lbs Height 56 in Development as shown in photograph Two small subcutaneous nodes on either side of neck in occipital region Visual fields normal Testes not palpable

Röntgenographic findings Floor of sella depressed and posterior clinoids decalcified Ventriculograms normal Bone age 11 years Lower end of left femur and upper end of right fibula show small areas of increased radiance and appear as cysts

Pathologic diagnosis Nodule—neurofibroma

Comment Roentgen findings and general physical status suggested craniopharyngioma however this could not be verified Neurofibromatosis with a neurofibromatous lesion adjacent to the sella could account for the whole picture

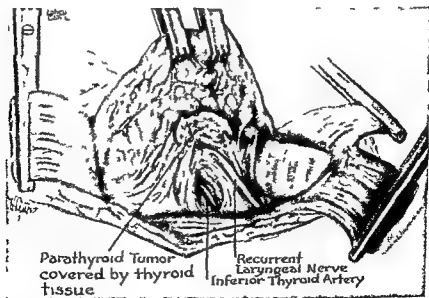


FIG 266 PARATHYROID ADENOMA DEEP BEHIND THYROID GLAND (Lahey F H and Haggart G E Hyperparathyroidism clinical diagnosis and operative technique of parathyroidectomy Surg Gynec & Obst 60 1033 1051)

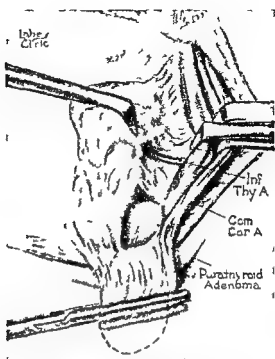
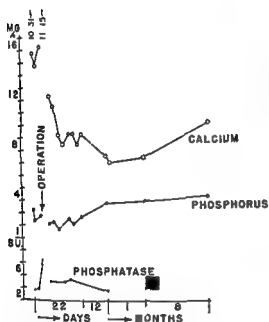


FIG 26. PARATHYROID ADENOMA DESIDE COMMON CAROTID AND BELOW INFERIOR THYROID ARTERY (Lahey F H and Haggart G E Hyperparathyroidism clinical diagnosis and operative technique of parathyroidectomy Surg Gynec & Obst 60 1033 1051)

CHART 84 HYPERPARATHYROIDISM DUE TO PARATHYROID ADENOMA Chart showing changes in serum calcium and phosphorus after removal of parathyroid adenoma Dihydroxycholesterol (AT 10) (solid black square) was used temporarily because of mild tetany. No bone changes were noted in this patient Chief complaint was stiffness in anterior thigh and calf muscles Findings before and after operation are listed below

	BEFORE OPERATION	3 TO 4 WEEKS AFTER OPERATION
Urine specific gravity	1 009 1 008 1 007 4 400 000	1 010 1 015 3 500 000
RBC	86%	76%
Hgb	40 mg %	31 mg %
NPN	6 4 Gm %	9 0 Gm %
Total plasma protein	4 4 Gm %	4 7 Gm %
Albumin	1 9 Gm %	4 3 Gm %
Globulin	15% (1/2 hr)	25% (1/2 hr)
PSP	43%	53%
Urea clearance test		

Some improvement in renal function within a month after operation

CHART 85 HYPERPARATHYROIDISM WITH RENAL INSUFFICIENCY PERSISTING AFTER CURE

Family history Negative

Past medical Negative

Chief complaint Pain in knees and legs

History of present illness On set 3 years previous after removal of stone from kidney

Physical examination Age 53 female married Weight 141 lbs Height 63 in BP 172/102 Dorsal round back Crepitation of knees

Laboratory data Urine al bumin 2 plus sugar absent, specific gravity 1 008 alkali line sediment 15 to 20 WBC Sulkowitch 1 plus PSP 15% excretion of dye RBC 3 490 000 Hgb 74% WBC 9 300 Blood NPN 63 mg % Serum calcium 14 4 mg % Serum phosphorus 3 6 mg % Serum alkaline phosphatase 46 B U Sedimentation rate 98 mm/hr

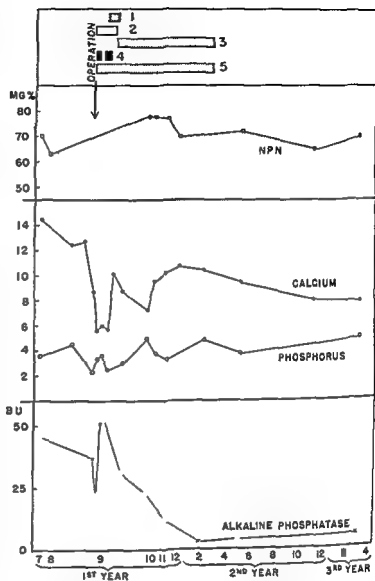
Roentgenographic findings Knees—decalcification with cystlike areas in lower femoral shaft Pelvis—marked osteitis fibrosa cystica Flat plate of abdomen—stones in left kidney

Treatment: Removal of parathyroid adenoma 3 1/4 cm in diameter Postoperative course—oliguria for several days No tetany with treatment

Progress BP 3 years after operation 128/100 Blood NPN 68 mg % Serum calcium 9 0 % Serum phosphorus 4 0 % Serum alkaline phosphatase 2 6 B U

Comment Taking calcium lactate and low protein salt free diet Doing well under care of a urologist

Symbols (1) AT 10—0 625 mg daily (2) Parathyroid extract—100 units daily (3) Vitamin D—50 000 units daily (4) Calcium gluconate—20 cc intravenously (5) Calcium lactate—180 gr daily



CHAPTER 5

Adrenals (SUPRARENALS)

PRECLINICAL

Section 39 PRELIMINARY

- I HISTORY
- II ANATOMY
- III EMBRYOLOGY
- IV CONGENITAL ANOMALIES
- V HISTOLOGY
- VI FUNCTIONS
- VII CHEMISTRY
- VIII BIO ASSAY
- IX PATHOLOGY
- X CLASSIFICATIONS
- XI CHIEF CLINICAL FINDINGS OF HYPOSECRETION
- XII CHIEF CLINICAL FINDINGS OF HYPERSECRETION
- XIII EXAMINATION OF PATIENT

CLINICAL

Section

- 40 ADDISON'S DISEASE
 - 41 WATERHOUSE FRIDERICHSEN SYNDROME
 - 42 ADRENOGENITAL SYNDROME
 - 43 FEMINIZING SYNDROME DUE TO MALIGNANT ADRENAL CORTICAL TUMOR
 - 44 HYPERFUNCTION OF ADRENAL MEDULLARY OR OTHER CHROMAFFIN TISSUE DUE TO PHEOCHROMOCYTOMA
-

SECTION 39

PRELIMINARY

I HISTORY

1564	Eustachius ²³	First description of adrenals
1629	Jean Riolan ² (The Younger)	Suprarenal capsules ⁷ was used for the adrenal glands
1651	Thomas Bartholinus Valsalva (1666 1723) ⁶⁸	Adrenals distinct from the kidneys, medulla recognized The adrenals were believed to be connected to the gonads by a duct
1736	Cook ¹⁸	A case of obesity excess hair and adrenal tumor was recorded (unverified)
1802	Bevan and Romkild ¹¹	Child described who looked like a woman Adrenal tumor found on postmortem examination
1816	Otto ¹⁶	Hypertrophy of the adrenals found in hypergenitalism
1824	Combe ¹⁷	Condition now known as Addison's disease reported
1839	Bergmann ⁹	Relation of the adrenal medulla to the nervous system was recognized
1840	Gulliver ²⁰	Sphenoidal bodies identified within the adrenals
1846	Echer ²²	Adrenal cells had a glandular function and secreted into the blood or lymphatics
1846	Goodsir ²⁸	Adrenals do not become distinct organs until testes ovaries and kidneys have appeared they retain the original texture of blastodermis
1849	Addison ³	First description of hypofunction of the adrenal glands
1856	Brown Séguard ¹⁴	Removal of adrenals was fatal in animals
1856	Vulpian ⁷⁰	Reaction for adrenaline in the adrenal glands
1865	de Crecchio ¹⁹	Adrenal hypertrophy described in a 40 year old female pseudohermaphrodite—an early case of adrenogenital syndrome probably initiated late in fetal life
1865	Henle ³²	Chromaffin reaction discovered and believed due to presence of adrenaline granules
1870	Heppner ³³	Hyperplasia of accessory adrenals located in broad ligaments and also normal adrenal glands were discovered in a 2 month old infant presumably male having a hypospadias penis prostate and ovaries without any follicles
1882	Goodhart ⁷	Simple atrophy of suprarenal capsules first reported
1889	Thornton ⁴⁴	First successful removal of adrenal tumor associated with hirsutism and mammary regression
1892	Berdez ⁸	Original report of a medullary tumor
1894	Voelcker ⁶⁹	Primary description of fulminating purpura with bilateral adrenal hemorrhage
1895	Moore ⁴³	Sphenoidal bodies (later called chromaffin) were related to pressor substances
1895	Oliver and Schafer ⁴	Pressor substance (adrenalin) was found in the adrenal medulla
1896	Fraenkel ⁵	Active principle of medulla was recognized
1897	Abel ¹	Pressor substance called epinephrine ⁷
1897	Neusser ⁴⁴	Medullary tumors are associated with hypertension
1901	Aldrich ³	Successful (independent of Takamine) isolation of crystalline adrenalin formula— $C_9H_{13}NO_3$ this was the first hormone to be isolated

1901	Little ³³	Adrenal apoplexy recognized
1901	Pepper ⁴⁷	A case with adrenal medullary tumor recorded
1901	Iakamine ⁶	Adrenalin isolated
1904	Stolz ⁶⁰	Lpinephrine synthesized
1905	Bulloch and Sequeira ¹	Adreno _o ental syndrome identified ✓
1907	Hutchison ³	Suprarenal sarcoma in children was studied
1909	Porges ¹	Hypo _o lycemic attacks occur in Addison's disease
1910	Apert ¹	Cases of adrenal hypertrophy (or 'hyp repinephric syndrome) summarized
1911	Stewart ⁹	Biolo _o ic tests for adrenalin in blood
1911	Waterhouse ⁷¹	All cases of adrenal hemorrhage and fulminating purpura were summarized
1914	Holmes and Sargent ³¹	Complete cure of a masculinized female due to benign adrenal tumor (first reported in 1924) Operation performed by Sargent
1915	Cannon ¹⁶	Theory of 'emergency function' of adrenals proposed
1916	Marshall and Davis ¹¹	Nonprotein nitro _o gen increased in adrenalectomized animals
1918	Friderichsen ⁶	Second summary of cases with adrenal hemorrhage and fulminating purpura (Waterhouse Friderichsen syndrome)
1919	Bittorf ¹¹	Clinical picture of feminism in males may be due to adrenal neoplasm
1922	Labbe Tinel and Doumer ⁸	First clear description of paroxysmal hypertension caused by pheochromocytoma
1926	Roux	Successful removal of pheochromocytoma, but blood pressures were not recorded
1926	Vaquez and Donzelot ⁶⁷	Clinical diagnosis of pheochromocytoma
1927	Baumann and Kurland ⁹	Sodium decreased and potassium increased with adrenal insufficiency (blood)
1927	Hartman MacArthur and Hartman ³¹	A substance (cortin) prolongs life of adrenalectomized cats
1927	Mayo ⁴	First successful exploration for cause of paroxysmal hypertension tumor removed with cure
1927	Rogoff and Stewart ⁴	A substance (interrenalin) increased the life span of adrenalectomized dogs
1928	Szent Gyorgy ⁶¹	Cevitamic acid found in adrenal cortex
1929	Pliffner and Swingle ⁴⁹	Method of preparing extract of adrenal cortex (first 'potent extract')
1929	Pincoffs ⁴⁰ and Shipley ⁶	First preoperative diagnosis of chromaffin tumor as cause of paroxysmal hypertension
1929	Rogoff and Stewart ³	Adrenal cortical extract (interrenalin) used in the treatment of Addison's disease
1931	Perla and Gottesman ⁴⁸	Cortinlike properties of urine demonstrated
1932	Loeb ¹⁰	Adrenal control of electrolyte metabolism studied
1933	Broster and Vines ¹³	Cortical cells of adrenals in virilism showed an abnormal red color with Ponceau fuchsin stain
1933	Harrop et al ⁶	Sodium chloride restriction precipitated crises in Addison's disease
1934	Kendall et al ³⁷	Crystalline form of cortin isolated

1935	Whitehorn	Chemical method for estimating epinephrine in blood
1936	Truszkowski and Zwerner ¹⁴	Low potassium diet advised for Addison's disease
1937	Beer, King and Prinzmetal ⁷	First demonstration of adrenalinlike pressor substance in the blood during an attack of paroxysmal hypertension
1937	Britton and Silvette ¹⁵	Carbohydrate metabolism role of adrenals analyzed
1937	Steiger and Reichstein ⁸	Desoxycorticosterone synthesized
1937	Young ³	Genital and adrenal abnormalities summarized
1938	Simpson ⁷	Synthetic desoxycorticosterone used for Addison's disease
1939	Ferrebee et al. ⁴	Desoxycorticosterone given by intramuscular injection for Addison's disease
1939	Thorn ⁶³	Treatment of Addison's disease with pellets of desoxycorticosterone
1940	Dijkhuizen and Behr ⁷⁰	Case of adrenal hyperplasia with Addison's disease and virilism reported
1944	Duncan Semans and Howard ¹	Pheochromocytoma with diabetes described, the latter was cured by removal of tumor
1945	Venning ⁶⁸	Demonstration of high urinary glycolytic steroids in pregnancy
1948	Hench and Kendall ³⁶	First injection of compound E in human for rheumatoid arthritis

II ANATOMY^{1, 4}

A LOCATION AND DESCRIPTION

- 1 The two suprarenals are
 - a Situated on the upper pole of each kidney (11th to 12th thoracic to 1st lumbar vertebrae)
 - b Yellowish or brownish yellow bodies
 - c Surrounded by alveolar tissue containing fat
 - d Invested by a tough capsule through which pass numerous fibrous processes and vessels

2 Right adrenal

- a Triangular shape bearing a resemblance to a cocked hat
- b Relationships
 - (1) In contact with liver
 - (2) Behind inferior vena cava
 - (3) In front of diaphragm
- c Peritoneal coverings
 - (1) Upper part of its lateral surface is devoid of peritoneum
 - (2) Inferior portion is covered by peritoneum reflected from the coronary ligament

3 Left adrenal

- a Crescentic shape
- b Relationships

- (1) Separated by peritoneum from cardiac end of stomach or spleen
- (2) In contact with pancreas and splenic artery

c Peritoneal coverings

- (1) Upper area of its anterior surface is lined by peritoneum of omental bursa
- (2) Lower area is devoid of peritoneum

B PARTS

1 External or cortex

- a Color
 - (1) Externally — red or yellowish brown
 - (2) On section — yellow or orange

b Stratified

c Firm

- d It forms the greater part of the gland (60 to 80% of total mass)

2 Internal or medulla

- a Dark brown due to the presence of a very abundant blood supply
- b Soft
- c Pulpy

C WEIGHT^{3, 4}

1 Considerable variations

- a Average — 6 to 8 Gm

- b Range—4 to 18 Gm
 ■ Left usually larger than right
- 2 A single gland is present occasionally, or the two glands may be fused as one
- 3 During life²
- | | PER CENT OF
BODY WEIGHT |
|----------------------|----------------------------|
| a Fourth fetal month | 0.46 |
| b Birth | 0.23 |
| ■ Adult | 0.01 |
- 4 Total volume is about 5 cc
- D SIZE (average, variable) ^{2 4}
- | | CM |
|-------------|-----|
| 1 Length | 4.5 |
| 2 Width | 3.3 |
| 3 Thickness | 0.5 |
- E BLOOD AND LYMPH SUPPLY
- 1 Arteries
- a Derivation from the
- (1) Aorta
 - (2) Inferior phrenic
 - (3) Renal
- b Very rich separate blood supply to cortex and medulla about 6 to 7 cc /Gm of tissue/min⁵
- 2 Veins
- a Near the anterior border of each gland there is a short furrow, the hilum from which the adrenal vein emerges
- b Right adrenal empties into the inferior vena cava
- c Left adrenal
- (1) Empties into the renal vein
 - (2) May open directly into inferior vena cava
- d Cortex has no marked venous system
- 3 Lymphatics
- a All drain into lumbar glands
- b Cortical—pass through the connective tissue septa with the blood vessels
- c Medullary—accompany the larger venules and form a plexus around central vein
- F NERVES
- 1 Numerous fibers form suprarenal plexus
- 2 Fibers from
- a Greater splanchnic (chief supply)
- b Renal plexus
- c Celiac
- (1) Plexus
 - (2) Ganglion
- d Vagus (questionable)

e Phrenic

f Lumbar sympathetic ganglia

3 Nonmyelinated type within gland

4 Medulla

a Richer supply than cortex

b Small ganglia and single neurons within parenchyma

III EMBRYOLOGY^{1, 2}

A CORTEX (origin from splanchnic mesoderm)

- 1 Four weeks (6 mm) There is a proliferation of epithelial cells which lie between the mesonephros and the root of mesentery
- 2 Six weeks (12 mm) The buds of tissue thus formed lie as a continuation of the suprarenal ridge
- 3 Birth Almost the entire gland is composed of cortical tissue

B MEDULLA (ectodermal origin, development according to weeks)

- 1 Three (9 mm) Ganglionated cord and sympathetic nerve plexuses
- 2 Six (16 mm) Visceral ganglia, cells give rise to chromophil tissue sympathetic chromophil tissue formed
- 3 Seven to 8 (20 mm) The sympathetic chromophil cells begin to migrate into the developing cortex along the central vein to form the medulla differentiation of the chromophil cells begins but is not complete until birth
- 4 After 8 Penetration of the epithelial anlage is accompanied

by a formation of folds and a process of invagination which results in more intimate contact of the medulla and cortex

- 5 Sixteen (121 mm) Chromaffin manufactures epinephrine, but not until after birth

IV CONGENITAL ANOMALIES

A CORTICAL TISSUE

- 1 Aplasia³
- 2 Hypoplasia

B MALFORMATION⁴

- 1 One adrenal only
- 2 Both glands fused as one
- 3 Kidney and adrenal wholly or partially within the same capsule

C ACCESSORY AND ABERRANT TISSUE^{4, 5}

- 1 Types
 - a Cortical tissue alone
 - b Cortical and medullary portions
 - c Medulla only (paraganglia)
- 2 Location
 - a Beneath the lower pole of kidney along spermatic artery
 - b Iliopsoas muscle
 - c Solar plexus
 - d Renal plexus
 - e Spleen
 - f Transverse colon
 - g Liver
 - h Pancreas
 - i Spermatic cord
 - j Epididymis
 - k Rete testis
 - l Ductus deferens
 - m Paradidymis
 - n Broad ligament³
 - o Fallopian tubes
 - p Ovaries
 - q Intercostal spaces
 - r Arteries¹
 - (1) Coronary
 - (2) Aorta
 - (3) Pulmonary
- 3 Outcome
 - a Common at birth but disappear

simultaneously with androgenic zone of adrenals during infancy

- b Hermaphroditism may develop
 - Later in life these may give rise to tumors which cause virilism in females
- d Pheochromocytoma

V HISTOLOGY (see Fig 268)^{1, 3}

1 CORTEX (3 zones are recognized the λ zone is still questionable)

- 1 Zona glomerulosa
 - a Layer immediately beneath the capsule
 - b Cells are arranged in groups with a suggestion of alveolar structure
- 2 Zona fasciculata
 - a Is continuous with glomerulosa portion
 - b Consists of columns of cuboidal cells arranged radially
 - c Comprises the greatest part of cortex
 - d Is rich in lipid material
 - e Changes during life span
 - (1) Childhood—narrow edge of tissue
 - (2) Puberty
 - (a) Width composed of 2 or 3 cells
 - (b) Cellular columns are long
 - (c) Cells firmly packed
 - (3) Maturity
 - (a) Cellular columns are shorter
 - (b) Cells are packed less closely
- 3 Zona reticularis
 - a Innermost zone lying next to medulla
 - b Cells
 - (1) Irregular loose arrangement
 - (2) Abundant fine droplets of lipid
 - c Changes in lifetime
 - (1) After second decade it contains pigment
 - (2) With aging
 - (a) Zone widens
 - (b) More vascular
 - (3) Late in life may equal the fascicular zone in size
- 4 λ zone (see 39 IV C)
 - a At birth there is a large zone (λ) between the
 - (1) Zona reticularis
 - (2) Medulla

- b This "fetal zone" undergoes involution during first year of life
- Significance is still a matter of controversy

B MEDULLA

- 1 Chromophil (chromaffin) cells
 - a Are scattered irregularly without any semblance of order
 - b Vary from cylindrical to irregular, polyhedral forms
- 2 Very vascular tissue
- 3 Sinusoids are interspersed throughout the intercellular meshes allowing intimate contact between the cells and the blood stream
- 4 Contents
 - a Nonmedullated nerve fibers in great abundance
 - b Sympathetic ganglia are found occasionally

VI FUNCTIONS

A GLAND AS A WHOLE

- 1 Although derived from entirely different embryologic tissue, the cortex and medulla are a unit anatomically
- 2 The cortex is under the control of the anterior pituitary, whereas the medulla apparently is not (see 2 VI B 9)
 - a The trend of evidence favors one adrenocorticotrophic hormone as regulating all adrenocortical functions
 - b The exact interrelationships or interdependence have not been fully determined
- 3 Cortex³
 - a Essential for existence, but precisely upon which functions or hormones life is absolutely dependent is still unknown
 - b Its functions must be numerous, many of which have yet to be discovered and even those known need more verification
 - (1) Carbohydrate metabolism is influenced in the manner that can only be inferred from the abnormal disturbances observed in adrenocortical syndromes and following injection of certain adrenocortical compounds or adrenocorticotropin²
 - (a) Some steroids may be held

within the adrenal gland to aid in the daily metabolic processes or for use under stress

- (b) Liver glycogen storage facilitated
 - (c) Sugar conservation by the tissues
 - (d) Protein conversion into sugar
 - (e) Defense mechanism
- (2) Evidence points to a role in immunity through the
 - (a) Release of gamma globulins
 - (b) Genesis of phagocytic cells
 - (3) Part played possibly by increased activity in
 - (a) Anoxia
 - (b) Abnormal internal or environmental temperatures
 - (c) Various intoxications as food or chemical poisoning
 - (d) A large group of damaging agents, including
 - [1] Surgical operations
 - [2] Anesthesia
 - [3] Injury
 - [4] Blasts
 - [5] Burns
 - [6] Congestive heart failure
 - (4) Bodily growth process is aided through anabolic effects⁴
 - (5) Control or sustenance of electrolytic balance is undoubtedly a continuous necessity
 - (a) One of the most important and vital functions
 - (b) Action on the renal tubules and sweat glands by promoting
 - [1] Sodium chloride retention
 - [2] Potassium excretion
 - (c) Blood pressure maintained
 - (d) Chief regulator of these leaving the medulla to act in emergencies
 - (e) Hyperactivity tends to preserve loss of electrolytes from excessive sweating and this accounts for acclimatization to high external temperatures

(f) Other functions may be conjectured on basis of the

[1] Changes occurring in abnormal states

[2] Role assigned to actions of known or supposed hormonal groups

(6) In the female, it influences or may be entirely responsible for sexual and body hair independent of its protein anabolic or androgenic influence

(7) It contributes to reproductive capacity, although this may be purely a secondary effect

(8) The following list of actions have also been postulated

(a) Lipoid (lipocorticoids) — stimulation of fat metabolism

(b) Trichogenic — sexual hair growth

(c) Antipigmentation

(d) Reproductive ['V' (?) hormone²]

(e) Bone maturation

(f) Estrogenic

(g) Renal

(h) Mammogenic

(i) Lactogenic⁷

4 Medulla

a General

(1) Not essential to life²

(2) Cardiovascular dynamics influenced

(3) Minor regulator of electrolytic balance

b Epinephrine may cause stimulation and release of pituitary adrenocorticotropin which is important in times of acute stress to protect the organism immediately and latently

(1) Acute stage through action of epinephrine or nor epinephrine upon the tissues (liver blood vessels, etc.)

(2) Chronic stage of resistance by the adrenocortical hormones

c Nor epinephrine

(1) Certain functions which are antagonistic to epinephrine

(2) No effect on adrenocorticotropin of pituitary⁸

B INDIVIDUAL HORMONES

1 Cortical hormones

a Introduction

(1) It is fairly certain that these are under pituitary control

(2) Current opinion leans toward the hypothesis that only one pituitary adrenocorticotrophic hormone (ACTH) maintains the secretion of all adrenocortical hormones (see 2 VI B 6)

(3) The number or exact nature of the hormones of the adrenal cortex is still unknown

(4) The cortex appears to influence many metabolic processes although our knowledge to date is still fragmentary

(5) Certain general actions are indicated by laboratory and clinical observations

(6) List of the possible hormones and their current terms

(a) Carbohydrate — sugar or S' glucocorticoids or anti-anabolic hormones (Compounds A B E F)

(b) Protein anabolic—nitrogen retaining or N, testoids or androgenic hormone (androsterone)

(c) Electrolytic — sodium potassium or water metabolic hormones or mineral corticoids (desoxycorticosterone) (see Table 47)

(d) Miscellaneous and hypothetical hormones which may or may not have been included

b 11 dehydrocorticosterone (compound A of Kendall) and 17 hydroxy 11 dehydrocorticosterone (compound E of Kendall)

(1) Animals (effect on intact rats using about 5 mg/24 hrs)

(a) Inability to use carbohydrate resulting in diabetes —insulin resistant²⁸

(b) Pancreatic diabetes intensified²⁴

(c) Gluconeogenesis varies⁵⁵

- (d) Glycogen deposited in liver of adrenalectomized mice⁷
8 4⁶ 5⁶
- (e) Weight⁴⁴
[1] Loss with compound E
[2] Gain with compound A
- (f) Increased urinary output of⁹
[1] Water
[2] Nitrogen
[3] Potassium
[4] Phosphorus (inorganic)
[5] Chlorides
[6] Ketones
- (g) Sodium retention
- (h) Growth inhibited⁴³ or sustained in adrenalectomized animals^{36 84}
- (i) Focal necroses in skeletal and cardiac muscles with calcification (mice)⁴⁸
- (j) Kidney size—increased⁴⁷
- (k) Resistance to stress increased^{35 4}
- (l) Lymphoid tissue lysis
- (m) Circulating eosinophils and lymphocytes decreased
- (n) Life maintained in adrenalectomized animals^{8 86}
- (o) Phosphatase content of bones is decreased⁸⁵
- (2) Humans with Addison's disease treated with compound A^{69 7}
- (a) Urinary excretion⁹
[1] Decreased
[a] Sodium
[b] Chloride
[2] Increased
[a] Water (may be decreased)
[b] Nitrogen (questionable)
[c] Potassium
[d] Phosphorus (not consistent)
- (b) It does not replace desoxy corticosterone (DOCA)
- (c) Equivalent to adrenocortical extracts
- (3) Effect on humans with compound E
(a) Changes listed under effects on animals (found in part at least)
- (b) Addison's disease
[1] Electrolytic balance maintained⁶
[2] No consistent changes in⁶⁹
[a] Phosphorus (urinary)
[b] Protein (serum)
[c] A/G ratio
[d] Blood lipoids
[e] 17 ketosteroids
[3] Increased urinary excretion of⁶⁹
[a] Sodium chloride (transient)
[b] Cortinlike substances
- (c) Sodium excretion may be increased when there is over treatment with desoxycorticosterone (DOCA)⁸
- (d) Diabetes may be intensified³
- (e) If anemia exists, there may be an increase in
[1] Red blood cells
[2] Hemoglobin
- (f) Alpha waves of electroencephalogram increase in frequency⁵
- (g) For therapeutic and toxic effects see 107 VIII F 1, M 2 a
- c 17 hydroxycorticosterone (compound F of Kendall) (effect in rats or normal or adrenal insufficient humans using 20 mg/24 hrs)^{8 79}
- (1) Urine—increased output (variable) of
(a) Nitrogen
(b) Sodium
(c) Potassium
(d) Phosphorus (inorganic)
(e) Chlorides
- (2) Circulating eosinophils and lymphocytes—decreased
- (3) Sugar (blood)—increased⁴⁹
- (4) Uric acid (serum)—increased
- (5) Phosphorus (inorganic, serum)—lowered
- (6) Resistance to stress—increased³
- d Adrenal cortical extracts (commercial) in
(1) Adrenal insufficiency (human)
(a) Liver glycogen—increased

- (b) Hypoglycemia—retarded
- (c) Conversion of protein and fat to carbohydrate enhanced
- (d) Blood pressure—elevated
- (e) Sodium—conserved
- (2) Adrenalectomized animals (see 39 VI C)
 - (a) Large doses are not toxic
 - (b) Animals maintained in perfect health
- e Desoxycorticosterone (animals and humans) ^{1 23 37 39 71 77 8 10}
 - (1) General health—improved
 - (2) Weight—increased by prevention of fat depletion⁷
 - (3) Blood pressure—elevated (more so in adrenal insufficiency; this may not be due to an increase in plasma volume)
 - (4) Carbohydrate metabolism—may be altered⁷
 - (5) Phosphatase content of bones—increased²⁴
 - (6) Urinary excretion—increased^{4 20 23, 60 62}
 - (a) Output
 - (b) Potassium
 - (7) Potassium (serum)—lowered if high^{4 24}
 - (8) Sodium and chloride (blood)—increased if low^{23, 28 29}
 - (9) Plasma volume—increased^{30 31}
 - (10) Toxic in excessive doses causing (see 40 VI D)¹³
 - (a) Sodium retention in excess
 - (b) Hypertension
 - (c) Cardiac enlargement
 - (d) Edema
 - (e) Tendon contractures²⁴
- f Amorphous fraction⁴⁸
 - (1) Devoid of carbohydrate effects
 - (2) Action largely on electrolytes
- (3) More potent than synthetic desoxycorticosterone
- (4) Rate of growth—may increase⁴³
- (5) Phosphatase content of bones—unchanged²⁴
- g Fat factor—deposition of fat may be regulated by the adrenal cortex^{21 67}
- 2 Medullary hormones
 - a. Epinephrine⁶³
 - (1) Vascular changes^{10 23 34 61 64}
 - (a) Peripheral resistance decreased
 - (b) Heart rate increased, then decreased
 - (c) Amplitude of heart beat and output increased
 - (d) Coronary vessels dilated in experimental animals²
 - (e) Systolic blood pressure only raised, later drops
 - (f) Pressor effect reversed by ergotamine
 - (2) Hyperglycemic action (see 103 I H 4)^{9 14 15, 27}
 - (a) Effect dependent on amount of liver glycogen
 - (b) Liver glycogen may be raised, after a serious depletion by formation of lactic acid (Cort cycle)
 - (c) Muscle glycogen changed into lactic acid for conversion to liver glycogen
 - (3) The following are increased
 - (a) Fat oxidation¹⁶
 - (b) Protein catabolism^{18 23}
 - (c) Heat production⁶
 - (d) Oxygen consumption¹
 - (e) Carbon dioxide formation²⁷
 - (f) Lactate output⁷
 - (4) Variable effects on the following depending on dosage and species
 - (a) Skin and mucous membranes¹¹

TABLE 47 ACTION OF VARIOUS STEROIDS ON SODIUM AND POTASSIUM EXCRETION⁷²

STEROID	HORMONE-LIKE ACTION	SODIUM	POTASSIUM
Desoxycorticosterone (DOCA) (synthetic)	Salt	Decreased	Increased
17 hydroxycorticosterone (isolated from adrenal cortex)	Carbohydrate metabolism	Increased	Increased
Testosterone (synthetic)	Androgenic nitrogen retaining	Decreased	Decreased

- (d) Glycogen deposited in liver of adrenalectomized mice⁷
 - 8 4² 33
- (e) Weight⁴⁴
 - [1] Loss with compound E
 - [2] Gain with compound A
- (f) Increased urinary output of⁹
 - [1] Water
 - [2] Nitrogen
 - [3] Potassium
 - [4] Phosphorus (inorganic)
 - [5] Chlorides
 - [6] Ketones
- (g) Sodium retention
- (h) Growth inhibited^{2 43} or sustained in adrenalectomized animals^{30 31}
- (i) Focal necroses in skeletal and cardiac muscles with calcification (mice)⁴⁸
- (j) Kidney size—increased¹⁷
- (k) Resistance to stress increased^{3 42}
- (l) Lymphoid tissue lysis
- (m) Circulating eosinophils and lymphocytes decreased
- (n) Life maintained in adrenalectomized animals^{8 88}
- (o) Phosphatase content of bones is decreased⁴⁸⁵
- (2) Humans with Addison's disease treated with compound A—^{69 75}
 - (a) Urinary excretion⁹
 - [1] Decreased
 - [a] Sodium
 - [b] Chloride
 - [2] Increased
 - [a] Water (may be decreased)
 - [b] Nitrogen (questionable)
 - [c] Potassium
 - [d] Phosphorus (not consistent)
 - (b) It does not replace desoxy corticosterone (DOCA)
 - (c) Equivalent to adrenocortical extracts
- (3) Effect on humans with compound E
 - (a) Changes listed under effects on animals (found in part at least)
- (b) Addison's disease
 - [1] Electrolytic balance maintained⁷⁰
 - [2] No consistent changes in⁶⁹
 - [a] Phosphorus (urinary)
 - [b] Protein (serum)
 - [c] A/G ratio
 - [d] Blood lipoids
 - [e] 17 ketosteroids
 - [3] Increased urinary excretion of⁶⁹
 - [a] Sodium chloride (transient)
 - [b] Cortinlike substances
- (c) Sodium excretion may be increased when there is over treatment with desoxycorticosterone (DOCA)⁸
- (d) Diabetes may be intensified³
- (e) If anemia exists, there may be an increase in
 - [1] Red blood cells
 - [2] Hemoglobin
- (f) Alpha waves of electroencephalogram increase in frequency³
- (g) For therapeutic and toxic effects see 107 VIII F 1, VI 2 a
- n 17 hydroxycorticosterone (compound F of Kendall) (effect in rats or normal or adrenal insufficient humans using 20 mg/24 hrs)^{80 79}
 - (1) Urine—increased output (variable) of
 - (a) Nitrogen
 - (b) Sodium
 - (c) Potassium
 - (d) Phosphorus (inorganic)
 - (e) Chlorides
 - (2) Circulating eosinophils and lymphocytes—decreased
 - (3) Sugar (blood)—increased⁴⁹
 - (4) Uric acid (serum)—increased
 - (5) Phosphorus (inorganic serum)—lowered
 - (6) Resistance to stress—increased³³
- d Adrenal cortical extracts (commercial) in
 - (1) Adrenal insufficiency (human)
 - (a) Liver glycogen—increased

C ADRENALECTOMY (see Chart 86)^{22 31}

1 There is a gradual development of the following

- a Anorexia
- b Vomiting
- c Bloody diarrhea
- d Profound muscular weakness probably due to⁴
 - (1) Large amounts of sodium
 - (2) Less than normal potassium

- e Salivation
- f Restlessness
- g Clonic movements
- h Stupor
- i Convulsions
- j Cessation of lactation
- k Anuria^{9 10 11 14}

2 Miscellaneous effects

- a No change in growth rate (rats)⁴³
- b Decrease in
 - (1) Body temperature^{16 34}
 - (2) Basal metabolic rate
 - (3) Blood pressure
 - (4) Blood volume⁴¹
 - (5) Rate of blood flow^{9 13 14}
 - (6) Polymorphonuclears¹³
 - (7) Sugar (blood) (see Table 101)
 - (a) Normal at times
 - (b) Level depends on duration of abstinence from food⁴
 - (8) Sodium (serum)
 - (9) Chlorides (serum)
 - (10) Carbon dioxide capacity
 - (11) Bicarbonate
 - (12) Glutathione
 - (13) 17 ketosteroids — excretion of 2 mg/24 hrs persists in males who have been castrated and adrenalectomized for carcinoma of prostate thus pointing to another source of their formation¹

c Increase in

- (1) Erythrocytes¹⁷
- (2) Hemoglobin
- (3) Lymphocytes⁴⁴
- (4) Hematocrit
- (5) Capillary permeability^{8 26 27}
- (6) Nonprotein nitrogen
- (7) Urea¹⁷
- (8) Protein (may be decreased)^{17 19}
- (9) Potassium⁴

(10) Calcium³

(11) Phosphorus

(12) Magnesium

(13) Oxygen capacity of blood^{9 10 13 14}3 Reaction to stress toxins chemical agents = increased¹⁸

4 Pathologic physiology

a Increased capillary permeability is assigned as the cause of blood plasma loss and the redistribution of water throughout the body

- (1) Body cells absorb water from interstitial spaces
- (2) Erythrocytes take water from plasma

b Renal excretion^{12 24}

(1) Decreased

- (a) Nitrogen
- (b) Potassium which is released by body cells resulting in an elevated plasma level
- (c) Ammonia

(2) Increased

- (a) Water
- (b) Sodium producing decrease in plasma concentration
- (c) Chloride
- (d) Bicarbonate

c Absorption of sugar from gastrointestinal tract is thought to be reduced (humans) but this has not been definitely proven^{4 36 37}

- (1) Liver glycogen is not produced from glucose or is retarded
- (2) Blood sugar is decreased
- (3) Sugar is burned for energy purposes rather than converted into
 - (a) Protein
 - (b) Fat
- (4) No abnormality occurs in animals if fed and maintained with salt

(5) Small intestinal reabsorption is markedly retarded for^{8 40}

- (a) Sodium
- (b) Potassium
- (c) Chloride

d Reaction to stress and other similar episodes is due to an alteration in adrenocortical lymphoid tissue relationship

- (b) Salivary glands¹
- (c) Muscles^{11 0}
 - [1] Bronchioles
 - [2] Intestine³
 - [3] Gallbladder¹⁰
 - [4] Bladder³
 - [5] Male genital organs
 - [6] Uterus (contraction in pregnant cat, relaxation in nonpregnant)¹⁰
- (d) Kidneys¹³
 - [1] Afferent arterioles—constricted
 - [2] Renal flow—decreased
 - [3] Output—reduced without affecting glomerular filtration
- (e) Circulating erythrocytes and leukocytes by^{3 3 0 6}
 - [1] Splenic contraction (variable)
 - [2] Bone marrow stimulation
- (f) Coagulation time³¹
- (g) Potassium (plasma)^{1* 17 4}
- (h) Blood volume¹⁰
- (5) Adrenocorticotropin effects may be enhanced⁶⁰
 - (a) Increase in urinary excretion of uric acid
 - (b) Decrease in
 - [1] Eosinophils
 - [2] Basophils
 - (c) 17 ketosteroids and 11 oxy steroids are not altered
- (6) Summary — sympathomimetic hormone
 - (a) Action on effector cells
 - (b) Sympathetic nervous system imitated
- b Nor epinephrine
 - (1) Vascular changes⁴
 - (a) Peripheral resistance increased
 - (b) Heart rate
 - [1] Unchanged
 - [2] Slowed
 - (c) Cardiac output—not altered
 - (d) Diastolic as well as systolic blood pressure raised
 - (e) Pressor effect not reversed by ergotamine
 - (2) Hyperglycemic action — one eighth as effective as epinephrine¹
 - (3) Adrenocorticotropic effect — no decrease in circulating eosinophils⁰
 - (4) Uterine muscle (nonpregnant cat)—not conspicuously relaxed⁴
 - (5) Oxygen consumption—increased[→]
 - (6) Lethal dose—one third as toxic as epinephrine³
- c Combined action of epinephrine and nor epinephrine⁴
 - (1) Vascular changes
 - (a) Mean arterial pressure falls slightly
 - (b) Cardiac output increased
 - (c) Peripheral resistance falls from levels produced by nor epinephrine alone
 - (2) Interpretation—vasoconstrictor action of nor epinephrine is blocked by epinephrine[→]
- d Comparison in normal and hypertensive persons—see Table 48

TABLE 48 . COMPARISON OF EPINEPHRINE AND NOR EPINEPHRINE INFUSION IN NORMAL AND HYPERTENSIVE PERSONS IN APPROPRIATE DOSAGE³

	EPINEPHRINE	NOR EPINEPHRINE
Normal	Less sensitive to compound Vasodilation Cardiac stimulation	More sensitive to compound Vasoconstriction No cardiac stimulation
Hypertensive	Greater vasodilation than normal Response similar to nor epinephrine induced hypertension in normals	Greater vasoconstriction than normal (decreased epinephrine suggested as cause due to failure of methylation of nor epinephrine)

- (b) Chromophilic reaction
- (2) Golgi apparatus changes during
 - (a) Inactivity—compact
 - (b) Activity
 - [1] Diffuse
 - [2] Ramifying
- (3) Ascorbic acid concentration
- (4) Lipids and ketosteroids
 - (a) Distributed in zona
 - [1] Glomerulosa
 - [2] Fasciculata, outer part
 - (b) Content as revealed by
 - [1] Sudan dye reaction
 - [2] Phenylhydrazine
 - [3] Schiff reagent
 - [4] Ammoniated silver nitrate
 - [5] Birefringence
 - [6] Acetone solubility
 - [7] Autofluorescence

b Summary

- (1) Zona glomerulosa may exist in dependent of the pituitary but certain sudanophilic material requires adrenocorticotropin
- (2) Zona fasciculata is entirely regulated by adrenocorticotropin
- (3) λ zone may possibly be controlled by LH

F ACTIVITY AT DIFFERENT PERIODS IN LIFE

1 Birth

a Size of adrenals

- (1) Large about one third that of a kidney, possibly because of stimulation by maternal and placental hormones
- (2) Rapid involution of cortex just after birth⁴

b Some writers have suggested that relative adrenal insufficiency may occur at this time³

c Urinary glycoenic hormones are absent⁵

2 Three months of age—adrenals are reduced one half their size at birth

3 Childhood—cortical (mineral) and glycoenic (S) hormones reach adult levels

4 Pubescence and puberty—effective secretion of certain cortical hormones cause

a Hair growth

b Bone maturation possibly

5 Adult

a Adrenal (each)

(1) Weight—about 11 to 10 Gm

(2) Size—approximately $\frac{1}{2}$ the size of a kidney

b Variations in histology and function according to the influences to which the adrenal gland is reactive

6 Pregnancy, lactation and menstruation

a Some cortical enlargement is likely⁶

b Cortical function—may be increased

c Urinary glycoenic hormones—increased⁶

7 Old age

a Some shrinking of the glands probably giving rise to the hypothetical 'adrenopause'

b Urinary 17 ketosteroids decline slightly, aside from those derived from the testes¹

G MISCELLANEOUS FACTORS INFLUENCING ADRENAL CORTICES (experimental and human)

1 Cortical enlargement (possibly) produced by³

a Menstruation

b Pregnancy

c Lactation

d Administration of

(1) Vitamin C

(2) Vitamin B

e Undernutrition

f High protein diet¹

2 Avitaminosis (guinea pig) may cause hemorrhagic changes in adrenals

3 Denervation of adrenal does not affect the cortex

4 Hibernation produces complete atrophy of both glands⁷

5 Cortical steroid and medullary chromaffin granules disappear during stress as with (see 99)³

a Burns

b Cold

c Muscular exertion

d Anesthesia

e Trauma

f Hemorrhage

g Chemical agents

h Poisons

i Acute infections

j Damaging factors

- e Fat metabolism is impaired
 - f Elevation of nonprotein nitrogen is partially due to late impairment of renal function
 - g Amino acids
 - (1) Deamination decreased
 - (2) Used for energy purposes probably
 - h Retardation of growth in animals may be related to loss of cortical androgenic influence plus other altered metabolic processes mentioned above which might discourage tissue synthesis^{1 7} (Immature adrenalectomized rats or dogs live and grow on high sodium chloride, low potassium diet²²)
 - i Gastric changes, as ulceration, are caused by a functional derangement in
 - (1) Motility
 - (2) Achlorhydria
 - j Lactation prevented¹
 - k Other findings are not explained so readily
- 5 Removal of medulla only is not followed by obvious insufficiency³⁹
- a Extra adrenal sources of epinephrine may be explanation
 - b Loss detectable in emergencies
- 6 Effect on other endocrine glands
- a Cortical hyposecretion or absence
 - (1) Pituitary—see 2 IV B 16
 - (2) Thyroid—no significant alterations, possibly increased activity, then decreased^{-6 27}
 - (3) Parathyroids—variable reports on serum calcium level^{1 43}
 - (4) Testes or ovaries may become atrophic^{28 38}
 - (5) Pancreas may show³
 - (a) Congestion
 - (b) Hemorrhage
 - b Medullary hyposecretion or absence retards adrenocorticotropin secretion
- D HYPERHORMONAL EFFECTS
- 1 On various organs and functions
 - a Cortical hormones summarized under
 - (1) Individual hormones—see 39 VI B 1
 - (2) Cushing's syndrome
 - (3) Adrenogenital syndromes
 - (4) Diabetes mellitus
 - (5) Steroid metabolism
 - b Medullary hormones summarized under
 - (1) Individual hormones—see 39 VI B 2
 - (2) Pheochromocytoma
 - 2 On other endocrine glands
 - a Cortical hormones
 - (1) Pituitary—see 2 IV B 17, 11 A B 1
 - (2) Thyroid—may depress function through pituitary^{1 4 6 7}
 - (3) Parathyroids—serum calcium may decrease¹⁰
 - (4) Gonads—'S' hormones may inhibit function
 - (5) Pancreatic islands—"S" hormones may inhibit insulin production or effectiveness
 - b Medullary hormones
 - (1) Insulin production or effectiveness may be inhibited^{3 8}
 - (2) Thyroid^{3 9}
 - (a) Iodine may be released
 - (b) Hyperplasia (possible)
- E HISTOPHYSIOLOGY
- 1 Origin of secretions
 - a Cortical hormones
 - (1) Zona glomerulosa is believed to elaborate steroids (desoxycorticosterone) which influence salt and water metabolism (see below)^{4 9-8}
 - (2) Zona fasciculata produces the carbohydrate (11 oxycorticosteroids, 'S' or sugar) hormones (see below)^{1 6}
 - (3) Zona reticularis is considered by some to show hyperplasia and eosinophilia in the adrenogenital syndrome and therefore is the source of the nitrogen (N) retaining hormone⁵
 - b Medullary hormones (epinephrine)—see 44 V B
 - 2 Adrenal cortices^{3 8}
 - a Cortical activity is related to
 - (1) Mitochondria (index of cell viability i.e., irregular size and poor staining may show that the cell is dying) by their
 - (a) Form

- (b) Chromophilic reaction
- (2) Golgi apparatus changes during
 - (a) Inactivity—compact
 - (b) Activity
 - [1] Diffuse
 - [2] Ramifying
- (3) Ascorbic acid concentration
- (4) Lipids and ketosteroids
 - (a) Distributed in zona
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b Bone maturation possibly

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- a Menstruation
- b Pregnancy
- c Lactation
- d Administration of
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 - (2) Vitamin B
- e Undernutrition
- f High protein diet¹

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3 Denervation of adrenal does not affect the cortex

4 Hibernation produces complete atrophy of both glands²5 Cortical steroid and medullary chromaffin granules disappear during stress as with (see 99)²

- a Burns
- b Cold
- c Muscular exertion
- d Anesthesia
- e Trauma
- f Hemorrhage
- g Chemical agents
- h Poisons
 - i Acute infections
 - j Damaging factors

VII CHEMISTRY

A ADRENOCORTICAL HORMONES (or derived compounds)

1 Nature

a Introduction

- (1) Extracts of the adrenal cortex contain compounds which produce various actions, but their full interrelationships have yet to be established^{8, 18}
- (2) The likelihood of more than one cortical hormone has been questioned, but the divergent clinical syndromes due to adrenal pathology favor the existence of multiple hormones
- (3) Twenty eight or more steroid compounds have been isolated from animal adrenal glands, but few of these have been recovered from human urine¹¹
- (4) Some of the steroids derived from the adrenal cortex are physiologically active in different degrees
- (5) While it is desirable to separate the various actions of the compounds, it is probable that there is considerable overlapping of effects¹⁰
- (6) Pituitary adrenocorticotrophic hormone when injected in normal humans produces characteristic changes of the three main groups of adrenal hormones—(1) to (3) below

b Groups of adrenal steroids

- (1) Carbohydrate action (S, sugar, glucoid or antianabolic hormones characterized by oxygen on eleventh carbon atom)
 - (a) Corticosterone
 - (b) 17 hydroxy 11 dehydrocorticosterone (synthesized)
 - (c) 11 dehydrocorticosterone (synthesized)
 - (d) 17 hydroxycorticosterone
- (2) Androgenic action (all rather feeble—"N," nitrogen protein anabolic or testoid hormone)
 - (a) Adrenosterone
 - (b) Androsterone

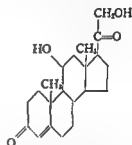
- ~(c) Dihydroandrosterone (11 hydroxyisoandrosterone)
- (d) 17 hydroxyprogesterone
- (3) Electrolytic action (salt, water and potassium hormones)
 - (a) 11 desoxycorticosterone
 - (b) Desoxycorticosterone (synthesized)
 - ~(c) 17 hydroxy 11 desoxycorticosterone
 - ~(d) Amorphous fraction
- (4) Estrogenic action³
 - (a) Estrone
 - (b) Estradiol
 - (c) Estrinol
- (5) Progestational action—progesterone

c Commercial extracts contain¹

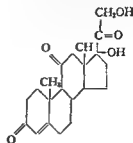
- (1) Various steroids which have carbohydrate as well as electrolytic action
- (2) Weak androgens
- (3) Estrogens
- (4) Progesterone

2 Formulas of certain cortical compounds

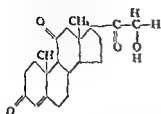
a Corticosterone (compound B—Kendall, H—Reichstein)



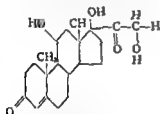
b 17 hydroxy 11 dehydrocorticosterone (compound E—Kendall, Fa—Reichstein, F—Wintersteiner and Pflüger)



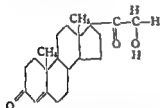
- 11 dehydrocorticosterone (compound A—Kendall)



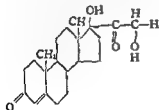
- d 17 hydroxycorticosterone (compound F—Kendall M—Reichstein)



- e 11 desoxycorticosterone (compound Q—Reichstein, DOC¹, DCA)



- f 17 hydroxy 11 desoxycorticosterone (compound S—Reichstein)



3 Properties

- a Desiccated suprarenal¹⁴
- (1) Form—amorphous powder
 - (2) Color—yellow to brown
 - (3) Odor—characteristic
 - (4) Solubility—partially in water
- b Desoxycorticosterone¹
- (1) Form—crystalline powder
 - (2) Color—white
 - (3) Odor—none
 - (4) Solubility

(a) Slight in vegetable oils

(b) Not in water

c Cortisone and hydrocortone

(1) Form—crystalline powder

(2) Color—white

(3) Solubility—slight in water

II ADRENAL MEDULLARY HORMONES

1 Nature

a Introduction

(1) Epinephrine was first isolated from the adrenals and later synthesized^{20 1}

(2) Nor epinephrine was first synthesized and later isolated from^{17 19}

(a) Cattle

[1] Adrenergic postganglionic nerves^{2, 21}

[2] Adrenal medullary extracts⁸

(b) Man—pheochromocytoma⁹

(3) Both are amines

(a) Epinephrine contains a methyl group, nor epinephrine does not

(b) Epinephrine may be methylated in the body from nor epinephrine⁴

(4) Both are sympathetic mediators^{6 23}

(a) Epinephrine—vasodilator

(b) Nor epinephrine—vasoconstrictor

b Commercial preparations

(1) Epinephrine or adrenalin chloride (synthetic, levo)

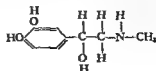
(2) U S P epinephrine (adrenal extract not sold commercially) contains³

(a) Epinephrine from 0 to 36 per cent

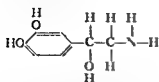
(b) Nor epinephrine from 64 to 100 per cent

2 Formulas

a Epinephrine (1 hydroxy 1 (3', 4 dihydroxyphenyl) 2 methylamino ethane adrenalin, suprarenine, levo)



- b Nor epinephrine 1 hydroxy 1 (3',4' dihydroxyphenyl) 2 aminoethane dihydroxyphenyl, arterenol levo active, dextro inactive)



3 Properties (epinephrine powder)¹³

- a Color—white or light brown
- b Odor—none
- c Taste—bitter
- d Activity destroyed by
 - (1) Copper
 - (2) Iron
 - (3) Zinc
 - (4) Other metals
- e Soluble in
 - (1) Water
 - (2) Alcohol
- f Insoluble in
 - (1) Chloroform
 - (2) Fixed and volatile oils
- g Solution—unstable
- h Dry form—stable
- i Oxidation retarded by excess acid
- j Decomposed by
 - (1) Air
 - (2) Light
 - (3) Heat

C HORMONE CONTENT IN BODY

1 Blood

- a Cortical hormones
 - (1) Peripheral—very small amounts
 - (2) With stress 1 cc of adrenal plasma may have 10 times the activity as that extracted from 1 Gm of gland¹⁶

b Epinephrine

- (1) Under resting conditions, concentration is less than one to one billion¹⁶
- (2) Peripheral venous blood contains 0000001 mg /l⁷

2 Gland—epinephrine

- a Content of both amounts to about 10 mg (fatal dose of this hormone is 2 mg if given intravenously or 8 mg subcutaneously)¹⁶
- b Total secretion per day is about 6 Gm (man weighing 60 kg)⁷

VIII BIO ASSAY

A CORTICAL HORMONES

1 Resistance to typhoid vaccine^{8 44}

- a Three month old adrenalectomized rats are given intraperitoneal injections of concentrated cortical extract (20 to 40 Gm daily)
- b Minimal lethal dose (MLD) of the rats to typhoid vaccine is determined
- c Rat unit—the quantity of cortical extract necessary to raise the resistance of adrenalectomized rats sufficiently to survive the MLD of typhoid vaccine injected on the sixth day postoperatively

2 Resistance to histamine⁴

- a Adult, adrenalectomized rats are killed by 100 to 200 mg of histamine (ergotamine acid phosphate)/kg when administered on the sixth day postoperatively (Normal rats survive 700 to 900 mg/kg)
- b MLD of histamine for adrenalectomized 6 week old rats is between 150 to 250 mg/kg of body weight
- c This is a better method than typhoid vaccine
- d Unit—the amount of cortical extract injected intraperitoneally into adrenalectomized, albino rats on fifth to sixth day postoperatively necessary to protect the animals against 200 mg of histamine

3 Maintenance of growth^{8 22 3 40 43}

- a Normal growth can be evidenced by the daily increase (of several grams) in weight
- b Injections of the cortical extract (from beef glands) are given intraperitoneally from first to seventh day to adrenalectomized 1 month old rats and growth is determined
- c Unit—the amount necessary to permit normal growth in a 40 to 50-Gm rat when given a single daily intraperitoneal injection
- d Growing animals require higher doses (relative to their size) than adults
- e Dogs cats or mice may be substituted

4 Performance of muscular work^{8 1 18}
31.33 42

- a Adrenalectomized and nephrectomized rats are standardized as to
 - (1) Weight
 - (2) Diet
- b A special apparatus is necessary for
 - (1) Stimulation of the muscles
 - (2) Recording results
- Cortical hormones are injected
 - (1) At the beginning of muscular stimulation
 - (2) Again 6 hrs later
- d Stimulation = continued either
 - (1) Until the muscle ceases to respond
 - (2) For a period of 24 hrs
- The total number of recorder revolutions* for the 24 hr period is taken as an index of the efficacy of treatment
- f Unit—the work equivalent of a 0.2 mg dose of 17 hydroxy 11 dehydrocorticosterone administered twice during the test
- g A standard dosage response curve is established with 17 hydroxy 11 dehydrocorticosterone which permits the interpolation of work per performance in units of the standard
- h Method is specific for detection and estimation of biologic activity characteristic of the 11 oxygenated cortical steroids

5 Survival after adrenalectomy

- a Dogs (adult)^{6 4 40 46}
 - (1) Animals are adrenalectomized in 2 stages
 - (2) Special care and diet are essential
 - (3) Hormone extract is given (0.5 cc/kg) in 2 equally divided doses twice a day
 - (4) Normal physiologic conditions are to be maintained as determined by
 - (a) Maintenance of body weight
 - (b) Blood nonprotein nitrogen (or urea)

- (5) Unit—minimum daily kilogram dose of cortical hormone necessary to maintain a normal physiologic [maintenance of body weight and blood level of NPN (or urea)] state in an adrenalectomized dog for a period of 7 to 10 days

- (6) Test may be modified by basing the assay on⁷

- (a) Appetite
- (b) Body temperature

b Rats^{7 9 36}

- (1) The number of days of survival after operation are determined
- (2) Comparison is made with a group receiving hormone injections daily
- (3) Unit—minimum dose of hormone which given subcutaneously daily for 20 days to 4 week old male rats (60 to 80 Gm) is sufficient to
 - (a) Protect at least 80 per cent of the rats
 - (b) Produce an average growth of at least 20 Gm for the 20 day period

c Other animals may be used^{8 57}6 Survival after exposure to low temperature^{8-10 40 49}

- a Male or female hooded adrenalectomized rats between 35 to 50 Gm
- b Twelve to 24 hrs after adrenalectomy food and water are removed and the rats are placed in the refrigerator at a temperature from -2° to -5° C
- c Nine treated and 9 untreated animals are taken
- d Hormone is administered subcutaneously in 3 doses with a period of 3 hrs between injections
- e Unit—the minimum amount necessary to maintain life of 2/3 of the treated rats at a time when 2/3 of untreated controls succumb
- f Test is fairly simple rapid and sensitive
- g Mice may be used instead

7 Augmented potassium excretion^{8 61}

- a Rats (dogs show similar effects), under certain established conditions

* Each recorder revolution represents approximately 4 cm of muscle shortening. Muscle is weighted with 100 Gm; therefore each recorder revolution indicates about 400 Gm cm of work.

following injections of cortical extract, have definite changes in excretion

- (1) Decreased
 - (a) Phosphate
 - (b) Sodium
 - (c) Chloride
- (2) Increased—potassium
- b Results are very inconsistent

8 Sodium retention^{1, 40}

- a Normal dogs must have special preparation and care in procedure
- b Unknown material can be dissolved in peanut oil or 10 per cent ethyl alcohol and given subcutaneously
- c Desoxycorticosterone standardized as follows
 - (1) Response of each test animal determined following the injection of a given dose (0.6 to 0.8 mg)
 - (2) If dose injected gives less than 35 per cent or more than 65 per cent retention of sodium the test is repeated using a modified dose
- d Sodium and chloride excretion are determined
- e The normal electrolyte excretion (control level) of dogs is established for the 6 hr test period
- f Control tests are done until the level is constant
- g Percentage of sodium retention is calculated using the average of 2 controls immediately preceding the test as the normal level
- h Unit—sodium retention defined as one tenth of the material which will cause equivalent sodium retention as 0.7 mg desoxycorticosterone in the same dog
- i Calculation may be made by formula

$$\text{No of units} = \frac{\text{Per cent retention by unknown}}{\text{Per cent retention by 0.7 mg}} \times 10$$

9 Resistance to water intoxication¹⁶

- a Adrenalectomized rats or dogs are used
- b Animals are fasted and then a calculated amount of water is administered by a stomach tube

- c Criteria of response determined by
 - (1) Rate of urinary excretion
 - (2) Occurrence of prostration
 - (3) Convulsions
 - (4) Death

d Various steroids are compared in this way

- e Hormones are given in divided doses
 - (1) Subcutaneously
 - (2) Intraperitoneally

f Minimal dose for life maintenance can be determined for adrenocortical compounds

10 Glycogen deposition in liver^{8, 9, 11, 35, 40-42, 47, 68}

- a Standardized adrenalectomized mice are needed
- b Injections are given subcutaneously at definite intervals
- c Each mouse receives a total of 1.4 cc of extract containing 70 mg of glucose
- d Livers are removed
 - (1) Glycogen is hydrolyzed
 - (2) Amount of glucose is determined
- e Glycogen is expressed in terms of mg of liver glucose/100 Gm of mouse body weight
- f Daily urinary excretion of corticoids in humans can be analyzed by this method
- g Rats may be used

11 Resistance to shock¹⁴

- a Adrenalectomized rats, 40 to 60 Gm which are tied down to a wire grid by all 4 legs for an hour develop shock and die in 4 hrs
- b DOCA adrenal cortical extract and certain 11 oxygenated corticosteroids prolong their survival
- c Typical dosage response curves may be obtained

12 Edema of perfused hind limbs^{30, 48}

- a Perfusion methods for assaying potency of adrenal cortical extracts are unsuitable
- b Frog and guinea pig hind legs are used
- c There is little reason to expect adrenal cortical extracts through effects on capillary permeability to decrease edema in perfused animal hind limbs

- d Method is not employed now
- 13 Eosinophilic or lymphocytic response³
- a Adrenocorticotropin injected
- b There is a decrease in circulating blood of
- (1) Eosinophils
- (2) Lymphocytes
- 14 Swimming test¹³
- a Rats with weights tied to their tails are immersed in water
- b Submerging under the water indicates exact moment of exhaustion
- c Adrenalectomized animals given cortin injections show an increase in swimming power
- d Comparisons can be made of the swimming time¹ under various conditions
- 15 Anti insulin—the various cortical principles can be compared by determining the insulin resistance (number of convulsions) of mice^{1 33}
- B MEDULLARY HORMONES**
- 1 Epinephrine
- a Epinephrine can be determined by many biologic and chemical methods even when present in minute quantities but none of the methods is specific
- b Intestinal strip method (most commonly used)—inhibiting action on strip of intestinal muscle (1 part epinephrine to 500 millions of solution)^{1 33}
- c Pressor changes in decerebrate cat^{22 2}
- d Perfusion through isolated limb or hind limbs of decapitated frog resulting constriction serves as a measure of epinephrine content^{27 33}
- e Auto-assay⁴
- (1) Reaction of animal's blood on its own organs
- (2) Epinephrine determined by any other method
- f Anastomatic procedure⁴
- (1) Adrenal vein of normal animal anastomosed to jugular of adrenalectomized dog
- (2) Changes in splenic volume or other effects are determined
- g Effect of drug on
- (1) Uterus¹
- (2) Denervated
- (a) Iris^{7 1} or excised eye¹
- (b) Heart^{19 60}
- ii Cava pocket¹ method⁴⁸
- (1) Amount of blood leaving adrenals/min
- (2) Concentration of epinephrine in this blood
- i Chromatographic methods—color reaction with^{1 17 18 20 39 9}
- (1) Ferric chloride
- (2) Ferricyanide
- (3) Iodine
- (4) Vanhydria
- (5) Persulfate
- 2 Nor epinephrine
- a Chromatographic methods—as above
- b Comparison with pharmacologic reactions of synthetic nor epinephrine or epinephrine nor epinephrine mixtures (see Table 48)²⁰
- IX PATHOLOGY**
- A Gross—see Table 49 (following page)
- B Microscopic
- 1 Atrophy—see 40 IX B 1 a
- 2 Hypoplasia—see 40 IX B 1 b
- 3 Tuberculosis—see 40 IX B 1 c
- 4 Amyloidosis—see 40 IX B 1 d
- 5 Hemochromatosis—see 40 IX B 1 f
- 6 Hyperplasia—see 42 IX B 1 a
- 7 Adenoma—see 42 IX B 1 b
- 8 Adenocarcinoma—see 42 IX B c
- 9 Pheochromocytoma—see 44 IX B 1
- C HISTOPATHOLOGY
- 1 Hypophysectomy^{2 6}
- a Fasciculata
- (1) Lipids and ketosteroids disappear
- (2) Mitochondria become smaller
- (3) Golgi nets are more compact
- b Glomerulosa—lipids and ketosteroids retained
- 2 Adrenocorticotropin injections or stress (see 2 VI B 6 99)³
- a Fasciculata
- (1) Mitochondria swell
- (2) Golgi net enlarges
- (3) Ketosteroid content
- (a) Initially—decreases
- (b) Later—increases
- (c) Terminally—disappears

TABLE 49 SURGICAL PATHOLOGY

	SIZE	APPEARANCE	CAPSULE	CONSISTENCY	LOCATION	EXTENSION
Cortex						
Adenomas	Barely discernible to large single or multiple	Red or yellow mass	Intact	Hyperplastic nodules soft	Cortex	Other adrenal may be aplastic
Hypoplasia	Slight to size of kidney	Normal	Intact	Firm	Usual except when accessory or aberrant gland	None
Carcinoma	Small to large	Gray or gray yellow often hemorrhagic smooth or multiple nodules	May be broken through	Soft	Cortex	Adrenal and renal veins invaded to lymph nodes liver lung brain and opposite adrenal via lymph or blood direct extension to kidney
Medulla						
Pheochromocytoma	Small to large	When small—reddish with thin layer yellowish cortical tissue attached large size—gray to brown often hemorrhagic or cystic	Preserved	Soft ruptures easily	Medulla of adrenal retroperitoneal area along aorta sacro coccygeal region carotid body other aberrant sites	If malignant directly by blood stream or lymphatics

- b Glomerulosa—no change
- 3 Desoxycorticosterone⁴
- a Fasciculata—no change
- b Glomerulosa—lipid and ketosteroid content disappears
- 4 Adrenocortical or 11 oxycorticosteroid⁵
- a Fasciculata—ketosteroid droplets disappear
- b Glomerulosa—no change
- 5 Testosterone (rats) ^a
- a Fasciculata—little effect
- b Glomerulosa—slight change
- c Reticularis—unaltered
- d X (male and female)—decreases especially in castrate animal
- 6 Estrogens⁷
- a Spayed guinea pig
- (1) Fasciculata—decreased
- (2) Glomerulosa—increased
- (3) Reticularis—increased
- b Rats (normal)
- (1) X zone¹
- (a) Male—reappearance of cells
- (b) Female—disappearance of cells
- (c) Lipoid substance produced
- (2) Gland (female) may increase⁹
- 7 Progesterone
- a Spayed guinea pig—all three zones are affected depending on amount administered
- (1) Small—increase⁷
- (2) Large—atrophy
- b Rats (female)—X zone shows no change⁵

X. CLASSIFICATION

A. COMPREHENSIVE LIST OF CHIEF FACTORS IN ENDOCRINE DISEASE—see 2 X A

B. HORMONAL (primary and secondary)

1 Hyposecretion

a. Cortex

- (1) Sugar (' S) hormones—Addison's disease
- (2) Nitrogen (' N) hormone
 - (a) Panhypopituitarism
 - (b) Addison's disease
 - (c) Primary myxedema
 - (d) Hyperthyroidism
- (3) Salt hormones
 - (a) Panhypopituitarism
 - (b) Addison's disease
- (4) Estrogens—hypopituitarism
- (5) Trichogens
 - (a) Primary myxedema
 - (b) Hyperthyroidism

b. Medulla—no known disease because of compensatory action of the sympathetic nervous system

2 Hypersecretion

a. Cortex

- (1) Sugar (' S) hormones—Cushing's syndrome
- (2) Nitrogen (' N) hormone—adrenogenital syndrome
- (3) Salt hormones—Cushing's syndrome possibly
- (4) Estrogens—feminizing syndrome
- (5) Trichogens
 - (a) Primary myxedema rare
 - (b) Menopause
 - (c) Hypertrichosis

b. Medulla epinephrines—paroxysmal or sustained hypertension in pheochromocytoma

3 Mixed—hyposecretion and hypersecretion

a. Cortex—adrenogenital syndrome with adrenal insufficiency due to hormonal

- (1) Sugar (' S)—decrease
- (2) Nitrogen (' N)—increase
- (3) Salt—decrease

b. Medulla—none recognized

C. CLINICAL

1 Hypofunction

a. Cortex

- (1) Addison's disease—primary cor

ticolysis¹ 42

- (2) Adrenal insufficiency secondary to pituitary disease

- (3) Congenitally small cortices

b. Medulla

- (1) No primary clinical syndrome has been recognized

- (2) Secondary to adrenal denervation (splanchnic resection)

c. Combined cortex and medulla

- (1) Addison's disease—classic

- (2) Adrenalectomy—removal of one gland when the other gland is

- (a) Nonfunctioning

- (b) Ab-ent

- (3) Congenitally small adrenals

- (4) Status thymicolymphaticus

- (5) Associated with hyperplasia of adrenogenital syndrome

2 Hyperfunction

a. Cortex

- (1) Cushing's syndrome (predominantly hypersecretion of "S" hormones)

- (a) Fetal

- (b) Prepuberal

- (c) Postpuberal

- (2) Adrenogenital syndromes (androgenic hyperadrenal corticalism)¹¹

- (a) Fetal

- [1] Early—pseudohermaphroditism (female)

- [2] Late

- [a] Masculinization in female without pseudomale external genitalia

- [b] Precocious male

- (b) Prepuberal

- [1] Masculinized female with enlarged clitoris

- [2] Precocious male

- (c) Postpuberal—virilism in female

- (3) Mixed entities

- (a) Cushing's syndrome combined with features of adrenogenital syndrome

- (b) Adrenal insufficiency and adrenogenital syndrome (included under hypofunction)

- (4) Feminizing syndromes (estrogenic hyperadrenal corticalism)—with the exceptions of feminization of the adult male and male pseudohermaphrodites, the following syndromes are more or less hypothetical^{2, 8}

(a) Fetal period

- {1} Female characteristics superimposed upon basically male organs—male pseudohermaphrodite

- {2} Precocious sexual development in female

(b) Prepuberal

- {1} Feminized boy

- {2} Precocious sexual development in female

(c) Adult

- {1} Feminized male

- {2} Hyperfeminized female⁽²⁾

- (5) Hypertrichosis* — excess hair growth in females without other masculinizing features

- b Medulla (hyperadrenalinism or hyperpinephrinism) — pheochromocytoma with paroxysmal or sustained hypertension

- c Mixed syndromes (hyperfunction and hypofunction)—adrenogenital syndrome and hypertension with pheochromocytoma^{4, 7}

D TUMORS*

I Types

a Cortical

- (1) Adenoma—nonmalignant
(2) Carcinoma

b Medullary

- (1) Pheochromocytoma
(a) Benign
(b) Benign metastasizing
(c) Malignant (5 to 10%)
(2) Neuroblastoma or sympathoblastoma of various types—malignant

- (3) Ganglioneuroma—benign

- (4) Mixed tumors containing any or all elements of above

■ Interstitial¹⁰

- (1) Sarcoma
(2) Lipoma
(3) Hemangioma
(4) Lymphangioma

2 Endocrine function

a Cortical tumors

- (1) No alteration
(2) Hyposecretion
(3) Hypersecretion

b Medullary tumors

- (1) No alteration
(2) Hypersecretion

c Interstitial cell

- (1) Usually no alteration
(2) Hypofunction—possible
(3) Hyperfunction—may be

XI CHIEF CLINICAL FINDINGS OF HYPOSECRETION

A CORTEX

- 1 Anorexia
2 Weight loss
3 Asthenia
4 Hypotension

B MEDULLA—None

XII CHIEF CLINICAL FINDINGS OF HYPERSECRETION

A CORTEX

- 1 Sugar (S) hormones
a Growth retardation in young
b Striae purplish
c Genital atrophy
d Osteoporosis
e Lympholysis
f Diabetes mellitus
2 Nitrogen ('N') hormone
a Growth acceleration in young
b Muscle mass—increased
c Acne
d Hypertrichosis
e Masculinization in varying degrees

3 Mineral hormones

- Hypertension
b Salt retention

B MEDULLA—Hypertension

* While this is familial and racial in many instances the presence of excess urinary 17 ketosteroids points sufficiently to cortical hyperfunction in regard to hair producing hormones to warrant its inclusion here

XIII EXAMINATION OF THE PATIENT

The divergent clinical syndromes caused by dysfunction of the adrenal glands renders no simple and satisfactory plan of examination

A HYPADRENOCORTICALISM OR ADDISON'S DISEASE (see 40 XII)

1 History of

- a Weakness
 - (1) Gradual
 - (2) Fairly rapid

b Anorexia

c Loss of weight

d Nausea

e Vomiting

f Diarrhea

g Abdominal pain

h Darkening of skin

i Loss of energy

j Familial tuberculosis

2 Physical status

a General

- (1) Languor often
- (2) Prostration in acute cases
- (3) Evidence of weight loss

b Skin

- (1) Loss of elasticity
- (2) Pigmentation
 - (a) Light tan or chestnut brown color
 - (b) Look for increased pigment on
 - [1] Exposed surfaces
 - [2] Points of friction
 - [3] Scars
 - [4] Tongue
 - (c) Inspect mucous membranes of lips and mouth for patchy pigmentation
 - (d) Black freckles (ink spots) are important

c Temperature is often subnormal in crisis

d Sexual hair in females

- (1) Is scanty
- (2) Regrows slowly when cut

e Heart sounds lack usual force

f Pulse is variable often thin

g Blood pressure

- (1) Variable usually low

(2) Normal or increased level in middle age does not exclude Addison's disease

h Splenic enlargement in some cases

i Lymph glands may be palpable especially after infection

j Muscular weakness can be demonstrated

3 Laboratory data

a Urinary chemical analyses⁷ 8

- (1) Sugar Absent or present with associated diabetes mellitus
- (2) Potassium Decreased
- (3) Sodium Increased, until body depletion occurs
- (4) Chlorides Increased until body depletion occurs

b Blood chemical analyses during crisis may be normal (because of hemoconcentration) or as follows⁷ 8

- (1) Sugar (fasting) Decreased
- (2) Nonprotein nitrogen Increased
- (3) Urea nitrogen Increased
- (4) Sodium Decreased
- (5) Potassium Increased
- (6) Chlorides Decreased
- (7) Carbon dioxide combining power Decreased

c Glucose insulin and glucose insulin tolerance tests (see 103 I J)

- (1) These are not necessary for routine diagnosis
- (2) Hypoglycemic reactions are due to insulin sensitivity therefore insulin administration must be given with caution

d Urinary hormone assays⁸ (see 107 II A C III IV)

- (1) 17 ketosteroids—very low an index of N hormone function
- (2) 11 oxyteroids—absent an index of S hormones

4 Roentgenographic findings

a Skull should be checked for possible pituitary tumor especially if there is no pigmentation of the skin or mucous membranes

b Chest for tuberculosis

c Abdomen for adrenal

- (1) Calcification
- (2) Tumor

5 Methods for special procedures

a Water test

- (1) Indication — for determination of mineral hormonal function?^{8 21}

(2) Part I (see Charts 87 and 88)

(a) Method and directions (based on volume of urine—modified so that patient can do it at home)

- [1] On day before test eat ordinary meals, but do not add salt to your food
- [2] Do not eat or drink after 6 00 P M
- [3] At 10 30 P M empty bladder, do not save the urine at this time
- [4] Collect all the urine from then on until and including that passed at 7 30 A M
- [5] Measure total urine in ounces
- [6] Omit breakfast
- [7] Drink 3 ounces of tap or warm water for each 10 lbs of body weight (example—if 120 lbs, drink 36 ounces)
- [8] Drink entire amount in 20 min
- [9] Note the time when all water is taken
- [10] Empty bladder at 1 2, 3 and 4 hrs after that
- [11] Lie down during entire test except to void
- [12] Collect each amount separately and measure in ounces
- [13] Bring in the record of
 - [a] Ounces of urine passed during night
 - [b] Ounces of urine passed at 1, 2 3 and 4 hrs

(b) Test is not accurate if patient

[1] Cannot drink the required amount of water

[2] Vomits

[3] Does not follow instructions correctly (when performed at home)

(c) Interpretation

[1] If the volume of any single urine specimen exceeds that of nocturnal amount, Addison's disease is probably absent

[2] If the volume of one of the day specimens is less than that voided during the night, Addison's disease may or may not be present

[3] If one specimen is below 100 cc, Addison's disease is very likely

[4] Part II is performed, if Part I is indefinite

(3) Part II

(a) Method (based on chemical composition of blood and urine)

[1] Part I is completed first

[2] Fasting blood sample is drawn (under oil preferably)

[3] Plasma is analyzed for

[a] Urea

[b] Chloride

[4] Night urine (10 30 P M to 7 30 A M) is analyzed for

[a] Urea

[b] Chloride

[5] Largest volume of day urine is used in calculation

[6] Equation for A*

(b) Interpretation

[1] Values for A which are greater than 30 indicate that patient probably does not have Addison's disease

$$*A = \frac{\text{Urea in night urine (mg/100 cc)}}{\text{Urea in plasma (mg/100 cc)}} \times \frac{\text{Chloride in plasma in (mg/100 cc)}}{\text{Chloride in night urine (mg/100 cc)}} \times \frac{\text{Volume of day urine (cc)}}{\text{Volume of night urine (cc)}}$$

- [2] Values for A which are less than 25 mean that Addison's disease is likely, providing nephritis has been excluded
- [3] If results are equivocal do salt deprivation test (see 39 XIII A 5 d)
- (4) Place of performance of test
- (a) Part I
- [1] Home
 - [2] Office
 - [3] Hospital
- (b) Part II
- [1] Office
 - [2] Hospital
- (5) Pathophysiologic considerations in chronic adrenal insufficiency
- (a) Part I—failure to excrete ingested water at normal rate may be due to
- [1] Faulty gastro-intestinal absorption
 - [2] Abnormal amounts of pituitary antidiuretic hormone in blood
 - [3] Imbalance of water distribution in body
 - [4] Impaired kidney excretion
- (b) Part II
- [1] Presence of azotemia is common
 - [2] Inability to retain sodium or chloride
- (6) Test may become negative in Addisonian patients when treated with Cortisone but not with desoxycorticosterone
- (7) Test may be positive in
- (a) Pituitary insufficiency
 - (b) Cushing's syndrome
 - (c) Myxedema (longstanding)¹⁸
 - (d) Hyperthyroidism
 - (e) Hyperparathyroidism osteitis fibrosa cystica and renal damage
 - (f) Normal people
 - (g) Anorexia nervosa
 - (h) Cachexia and allied disorders
 - (i) Prolonged febrile illness
 - (j) Sprue
 - (k) Postgastrectomy
 - (l) Acute rheumatoid arthritis
 - (m) Renal disease
 - (n) Postsympathectomy (dorsolumbar)¹⁴
 - (o) Orthostatic hypotension
 - (p) Hepatic cirrhosis
 - (q) Chronic calculous cholecystitis
 - (r) Psychopathic personality
 - (s) Neurologic disorders
- b Epinephrine test for anterior pituitary adrenocorticotrophic response^a
- (1) Method
- (a) No food is taken after 8 PM
 - (b) In the morning under fasting conditions a control eosinophil count is done on venous blood
 - (c) Five cc of venous blood is drawn into a bottle containing special solution to prevent distortion of red cell volume
 - (d) Solution

Ammonium	
oxalate	1.2 Gm
Potassium oxalate	0.8 Gm
Add distilled	
water to	100 cc
 - (e) After obtaining sample shake immediately and gently
 - (f) Specimen may be stored at temperature of 4° C up to 12 hrs
 - (g) Epinephrine hydrochloride injected either
 - [1] Intravenously over 1 hr—0.2 mg or 0.2 cc of 1:1000 in 200 cc of saline
 - [2] Subcutaneously—0.3 cc
 - (h) Sample is drawn 4 hrs after the beginning of the administration of epinephrine
 - (i) Food is taken after the test
 - (j) Eosinophil count technic

[1] Special diluting solution

- [a] Eosin (aqueous) 2 per cent 5 cc
 Acetone 5 cc
 Distilled water sufficient to make 100 cc

[b] Refrigerate and filter before use

[2] Oxalated venous blood is drawn into a white cell count pipet up to the 0.5 mark

[3] Pipet is shaken immediately gently only 50 times

[4] Chamber is filled with special solution

[5] Eosinophils counted after 3 min

- [a] Levy chamber having a depth of 0.2 mm and ruled area of 16 sq mm is used

[b] Average of 4 chamber counts is determined

[c] Number of eosinophils per cubic millimeter equals 6.25 times the average chamber count

(2) Interpretation (see Chart 89)

- (a) Patients with either Addison's disease or anterior pituitary insufficiency fail to show a decrease of 50 per cent or more in circulating eosinophils

- (b) Acute allergy may prevent an adequate fall because of a rapid replacement by a hyperplastic bone marrow

- (c) Complete reliance upon test is to be avoided

(3) Contraindication — arteriosclerotic cardiovascular disease

■ Adrenocorticotropin (ACTH) test (Thorn) for adrenal cortical function of "S" hormones^{15, 20}

(1) Method

- (a) No food is given after 8:00 P.M. on the day preceding the test, but water may be taken as desired

- (b) On the day of the test, 200 cc of water is given at

[1] 6:00 A.M.

[2] 8:00 A.M.

[3] 10:00 A.M.

- (c) Urine specimen is collected from

[1] 6:00 A.M. to 8:00 A.M. (control)

[2] 9:00 A.M. to 12:00 P.M.

- (d) Eosinophil count (see 4 c) is done at

[1] 8:00 A.M.

[2] 12:00 P.M.

- (e) Twenty-five mg of purified adrenocorticotrophic hormone is injected intramuscularly at 8:00 A.M. (after obtaining eosinophil count)

- (f) There are no reactions except blanching of the skin and mild intestinal cramps due to the contamination with oxytocic principle

(g) Urine specimens

- [1] Analyze by any standard method for

[a] Uric acid

[b] Creatinine

- [2] Compute the percentage change in uric acid creatinine ratio

- [3] Normal mean fasting uric acid creatinine ratio

[a] Male 0.43

[b] Female 0.59

[c] Mean 0.50

[d] Mean deviation 0.17

- (h) Eosinophil count technique (as above)

(2) Interpretation (see Chart 90)

- (a) Too much reliance should not be placed upon eosinophilic response due to inaccuracy of counting cells by

- [1] Inexperienced technician
- [2] Other factors possibly
- (b) Adequate adrenal cortical response if there is
 - [1] A fall of 30 per cent or more from the initial level of eosinophils
 - [2] An increase in the uric acid-creatinine ratio to a level above 50 per cent of the control
- (c) Variations in initial eosinophil count do not affect percentage of fall except during height of allergic eosinophilia when production exceeds peripheral destruction of eosinophils
- (d) False positives due to uric acid changes with
 - [1] Decreased renal clearance
 - [2] Abnormally high production of uric acid (gout leukemia)
- (e) Any condition causing acute stress may call out reserve of adrenal cortex and so gland cannot respond to further stimulation
- d Salt deprivation test for mineral hormone function⁷ *
 - (1) Method
 - (a) Low sodium diet for 3 days
 - [1] Chloride 0.95 Gm
 - [2] Sodium 0.59 Gm
 - [3] Potassium 4.10 Gm
 - (b) First day
 - [1] Free fluid intake
 - [2] In afternoon extra potassium (as citrate)
 - [a] Dose represents 0.033 Gm of potassium for each kilo gram of body weight
 - [b] To convert potassium to grams of potassium citrate multiply by 2.8
 - (c) Second day
 - [1] Forty cc of liquid is taken/kg of body weight
 - [2] Repeat dose of potassium citrate
 - [3] Blood sample is taken in an oiled syringe at 8.00 A.M.
 - [4] Urine collected from 8.00 A.M. to 8.00 P.M.
 - (d) Third day
 - [1] Twenty cc. of liquid/kg of body weight is taken by 11.00 A.M.
 - [2] Blood sample is drawn in an oiled syringe at 10.00 A.M.
 - [3] Urine collected from
 - [a] 8.00 P.M. to 8.00 A.M.
 - [b] 8.00 A.M. to 12 N.
 - (2) Results
 - (a) Blood plasma values for chloride sodium and potassium overlap those of the controls and so of little diagnostic value
 - (b) Concentration of chloride in urine of morning on third day is the most diagnostic part of test
 - [1] Addison's disease or adrenal insufficiency show values over 225 mg % (range 229 to 356)
 - [2] Adrenal insufficiency is unlikely in values less than 125 mg % (range 17 to 141)
 - [3] Values between the two
 - [a] Continue with restricted intake of sodium chloride
 - [b] Increase amount of potassium to equal a total of 9 Gm/24 hrs for 3 additional days or until crisis develops
 - (c) Urinary sodium of the third morning specimen (8.00 A.M. to 12.00 NOON) can be used for diagnosis
 - [1] Addison's disease—values of 206 mg % (range 165 to 282)

- [1] Special diluting solution
 - [a] Eosin (aqueous) 2 per cent 5 cc
 - Acetone 5 cc
 - Distilled water sufficient to make 100 cc
 - [b] Refrigerate and filter before use
- [2] Oxalated venous blood is drawn into a white cell count pipet up to the 0.5 mark
- [3] Pipet is shaken immediately, gently, only 50 times
- [4] Chamber is filled with special solution
- [5] Eosinophils counted after 3 min
 - [a] Levy chamber having a depth of 0.2 mm and ruled area of 16 sq mm is used
 - [b] Average of 4 chamber counts is determined
 - [c] Number of eosinophils per cubic millimeter equals 6.25 times the average chamber count

(2) Interpretation (see Chart 89)

- (a) Patients with either Addison's disease or anterior pituitary insufficiency fail to show a decrease of 50 per cent or more in circulating eosinophils
- (b) Acute allergy may prevent an adequate fall because of a rapid replacement by a hyperplastic bone marrow
- (c) Complete reliance upon test is to be avoided

(3) Contraindication — arteriosclerotic cardiovascular disease

- Adrenocorticotropin (ACTH) test (Thorn) for adrenal cortical function of "S" hormones^{15, 20}

(1) Method

- (a) No food is given after 8:00 P.M. on the day preceding the test, but water may be taken as desired
- (b) On the day of the test, 200 cc of water is given at
 - [1] 6:00 A.M.
 - [2] 8:00 A.M.
 - [3] 10:00 A.M.
- (c) Urine specimen is collected from
 - [1] 8:00 A.M. to 8:00 A.M. (control)
 - [2] 9:00 A.M. to 12:00 noon
- (d) Eosinophil count (see 4 c) is done at
 - [1] 8:00 A.M.
 - [2] 12:00 noon
- (e) Twenty-five mg of purified adrenocorticotrophic hormone is injected intramuscularly at 8:00 A.M. (after obtaining eosinophil count)
- (f) There are no reactions except blanching of the skin and mild intestinal cramps due to the contamination with oxytocic principle
- (g) Urine specimens
 - [1] Analyze by any standard method for
 - [a] Uric acid
 - [b] Creatinine
 - [2] Compute the percentage change in uric acid creatinine ratio
 - [3] Normal mean fasting uric acid creatinine ratio

[a] Male	0.43
[b] Female	0.59
[c] Mean	0.50
[d] Mean deviation	0.17
- (h) Eosinophil count technic (as above)

(2) Interpretation (see Chart 90)

- (a) Too much reliance should not be placed upon eosinophilic response due to inaccuracy of counting cells by

- [2] Incision 2 to 4 cm
- [3] Pockets prepared radially from incision by blunt dissection 2 to 3 cm in depth
- [4] One pellet implanted in each pocket after inspecting for bleeding
- [5] Incision closed with black silk

II ADRENOGENITAL SYNDROMES (see 42 \III)

1 History

- a Age of onset
- b Spurts of growth
- c Weight—gain common
- d Voice—changes
- e Hair growth—abnormal
- f Muscular feats—unusual for age
- g Psyche—altered
- h Sexual pattern—changed
- i Possible evidence of adrenal insufficiency, but with physical manifestations of adrenogenital syndrome

2 Physical status

- a Bodily contour generally masculine in type but feminization of males is a rare exception
- b Weight variable increased in most cases
- c Height age
 - (1) Advanced in childhood
 - (2) Retarded if sexual maturity occurs before usual age
- d Acne
- e Hair growth
 - (1) Abnormal
 - (2) Precocious
- f Breasts enlarge

III Blood pressure

- (1) Normal
- (2) Increased
- b Abdominal tumor may be found
 - i Genitalia
 - (1) Hypertrophy
 - (2) Atrophy of external organs (males)

3 Laboratory data

- a Blood chemical analyses reveal nothing unusual unless the syndrome is a mixed type
- b Urinary hormone assays
 - (1) 17 Ketosteroids
 - (a) Increased in majority

- (b) Greater increase (over 50%) in beta fraction with tumors than in hyperplasia (under 50%)¹⁹

- (c) Dehydroisoandrosterone is found in tumors rather than with hyperplasia¹

- (2) 11 oxysteroids—normal¹⁹

4 Roentgenographic findings

- a Skull—in children with precocious development to exclude
 - (1) Pinealoma
 - (2) Other intracranial disease
- b Hand wrist for bone age
- c Pyelograms for
 - (1) Kidney displacement
 - (2) Adrenal tumor
- d Air insufflation for outlining adrenal tumor or enlargement by presacral technic of Blackwood⁶ is safe and satisfactory

C. PHEOCHROMOCYTOMA (see 44 \III)

1 History for episodes of unusual character

- a Pounding headache
- b Sweating
- c Palpitation
- d Substernal distress
- e Tremor
- f Apprehension
- g Duration—5 min to 16 hrs

2 Physical status

- a During attack—see 44 \II
- b Blood pressure may be
 - (1) Normal
 - (2) Elevated with
 - (a) Ocular fundi showing vascular changes as found in hypertension
 - (b) Cardiac enlargement
 - (c) Gallop rhythm possibly
- c Adrenal tumor may be palpable 12 per cent are outside adrenal area²²
- d Precipitation of attack by palpation or massage of tumor site

3 Laboratory data

- a Findings during acute paroxysm—see 44 VII
- b Routine urine and blood chemical analyses are usually not helpful, except to point to chronic vascular nephritis in cases with sustained hypertension

- [2] Control group—values of 22.4 mg % (range 6 to 85)
 - [3] More difficult to do in most laboratories, and therefore chloride determination is utilized
 - (3) Dangers—adrenal crisis may develop, and therefore test should be performed in hospital
 - (a) Intravenous injection should be
 - [1] On hand for emergency
 - [2] Given at end of each test
 - (b) Solution of 1,000 cc sterile water with

[1] Dextrose	50 Gm
[2] Sodium chloride	10 Gm
[3] Sodium citrate	5 Gm
[4] Cortical extract	20 cc
- Potassium tolerance²⁰
- (1) Indication—aid in doubtful cases of adrenal cortical insufficiency
 - (2) Method
 - (a) No breakfast
 - (b) Blood sample collected to determine fasting serum potassium
 - (c) Dosage of potassium salt to be taken orally is 10 mg / kg of body weight
 - (d) Blood samples are collected every half hour for two hours
Caution—severe crisis may occur!
 - (3) Results
 - (a) Normal—20 to 40 mg % increase in $\frac{1}{2}$ hr, with a return to normal by $1\frac{1}{2}$ to 2 hrs
 - (b) Adrenal insufficiency—much greater rise and stays there for longer period
 - (c) Inconstant
- f Techniques for pellet implantation¹⁷
- (1) Locations—in subcutaneous tissue of
 - (a) Anterior thighs
 - (b) Abdomen
 - (c) Axillae
 - (d) Infrascapulae
 - (2) Methods
 - (a) "Medical" (office procedure) (see Fig 269)
 - [1] Skin prepared with
 - [a] Iodine
 - [b] Alcohol
 - [2] Intradermal infiltration of area of incision with procaine
 - [3] Subcutaneous infiltration for 3 to 4 cm in region of trocar thrusts
 - [4] Incision $\frac{3}{8}$ to $\frac{1}{2}$ in
 - [5] Abdominal or hydrocele trocar thrust in lower subcutaneous region horizontally for 3 in
 - [6] Stilet withdrawn
 - [7] Pellets
 - [a] Dipped in sterile saline
 - [b] Rolled lightly in sulfa powder
 - [8] One pellet
 - [a] Inserted into lumen of trocar
 - [b] Pushed through with stilet
 - [9] Trocar withdrawn $\frac{1}{2}$ to 1 in then second pellet implanted
 - [10] Only 2 pellets are implanted in 1 pocket
 - [11] New pockets are made in other directions if additional pellets are to be inserted at this time
 - [12] Incision edges are approximated by drawing skin tightly with a strip of adhesive which is applied transversely
 - [13] Thick gauze pad is placed over adhesive holding edges together
 - [14] Dressing and adhesive are removed in 4 to 5 days
 - (b) Surgical
 - [1] Skin prepared and infiltrated as above

- [1] Patient should be reclining
 - [2] Blood pressure cuff is placed on opposite arm
 - [3] Measurements of blood pressure taken several times 1 min apart before test drug is given
 - [4] Blood pressure is allowed to stabilize (20 min or so)
 - [5] Intravenous saline drip is started slowly through a 3 way stop cock
 - [6] Dose of dioxobenzane = 10 mg/sq meter body surface same as for basal metabolic rate or 0.25 mg/kg of body weight
 - [7] Dioxobenzane solution introduced through 3 way stop cock taking 2 min to inject it
 - [8] Blood pressure readings are then taken at
 - [a] One half min intervals for 5 min
 - [b] One min intervals until blood pressure returns to normal
- (b) Dibenamine test^{9 10 31}
- [1] Procedure as above
 - [2] Dosage
 - [a] Five to 7 mg/kg of body weight
 - [b] Maximum regardless of weight is 500 mg
 - [3] Dibenamine is added to 300 to 500 cc of saline
 - [4] Rate of flow—total dose should take 1 hr (not over 8 cc/min)
 - [5] Blood pressure readings as above
 - [6] If pressure falls significantly stop solution especially if near normal levels
 - [7] Effect of drug may last several days
- (6) Interpretation (see 39 VI B 2)
- (a) Dioxobenzane test (see Chart 93)
 - [1] Effect of circulating epinephrine is neutralized with a resulting fall in blood pressure
 - [2] Extent of drop is thought to parallel the amount of circulating epinephrine
 - [3] Small initial drops in pressure lasting up to 2 min are not significant
 - [4] Positive test is probable when there is a sustained fall in pressure lasting at least 7 min
 - [5] If the blood pressure is plotted on square millimeter paper against minutes the area included below the base line of the initial blood pressure may be expressed in millimeter minutes
 - [6] False negative tests—certain cases of pheochromocytoma fail to show a decrease in blood pressure^{11 12}
 - [7] False positive result—one reported diagnosis not proven⁷
 - (b) Dibenamine test (see Chart 92)
 - [1] Positive test when there is a significant lowering of pressure
 - [2] Experience with this preparation is limited
 - (7) Toxic and undesirable reactions
 - (a) Dangerous reactions are possible hence care should be exercised in administering these preparations
 - (b) Dosages recommended probably should be reduced on first trial of these drugs in order to test response
 - (c) Reactions⁹
 - [1] Marked rise in hypertensive patients of systolic and diastolic blood pressures
 - [2] Palpitation
 - [3] Tachycardia
 - [4] Precordial pain

- Basal metabolic rate is elevated when blood pressure is increased
- d Urinary hormone assay for epinephrine and nor epinephrine¹⁰
 - (1) Normal—20 to 40 micrograms/24 hrs
 - (2) Pheochromocytoma—up to 1,240 micrograms/24 hrs
- 4 Methods for special procedures
 - a Induction of paroxysm of hypertension by use of drugs^{4 5 14 15}
 - (1) Comment
 - (a) The danger of using certain drugs in patients with pheochromocytoma has frequently been pointed out and should be avoided in
 - [1] Severe cases
 - [2] Elderly people
 - (b) Basal blood pressure should be obtained first
 - (c) Avertin rectal anesthesia may be used to eliminate emotional variations in pressure
 - (d) Readings are taken at intervals of 1 min for 20 min
 - (e) False negatives and false positives may occur
 - (2) The following have been given to provoke an attack
 - (a) Adrenalin
 - [1] One to 1½ cc (1:1000) subcutaneously
 - [2] Induction of hypertension is possible although unusual resistance to this drug may exist³
 - (b) Histamine acid phosphate or hydrochloride⁴
 - [1] Dilute 1 cc of this solution in 9 cc of water
 - [2] Inject ¼ or ½ cc (0.025 or 0.05 mg) intravenously
 - [3] Antidote—adrenalin ½ cc intravenously
 - (c) Mecholyl (acetyl β methyl choline chloride—see Chart 91)¹¹
 - [1] Twenty five mg subcutaneously in forearm (below BP Cuff)
 - [2] For severe reaction
 - [a] Atropine sulfate gr ⅛ intravenously
 - [b] Blood pressure cuff or tourniquet should be applied to prevent further absorption
 - (d) Etamon (tetraethylammonium bromide or chloride)⁹
 - [1] Three cc intravenously, supine position*
 - [2] Instead of a sustained drop in blood pressure, a fluctuating fall followed by a rise may take place if pheochromocytoma is present
 - [3] Adrenalin (½ cc intravenously) may be used for postural hypotension
 - (e) Insulin tolerance test—may be helpful if diabetes is present (see 103 I J 2)
 - b Anti epinephrine tests
 - (1) Indications
 - (a) Differentiation of hypertension due to pheochromocytoma from other types
 - (b) Prevention of hypertensive crisis on manipulation or removal of pheochromocytoma
 - (2) Several preparations are available whose actions are chiefly adrenergic
 - (3) Pharmacologic action is to produce a high degree of reversible block to the stimulation of the adrenergic receptor cells to sympathetic nerve impulses or epinephrine
 - (4) Preparations
 - (a) Dioxobenzane (benzodioxane benodaine 2 [1 piperidylmethyl] 14 benzodioxane or 933 F)
 - (b) Dibenamine (N,N dibenzyl β chloroethylamine hydrochloride)
 - (5) Technics^{2 3 12 13 16 27}
 - (a) Dioxobenzane test

* Patient should not stand during procedure or until weakness is gone. An increase or decrease in blood pressure level may be regulated by lying or sitting position.

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- [5] Hyperpnea
- [6] Headache
- [7] Fright
- [8] Nervousness
- [9] Cold extremities
- [10] Flushing
- [11] Nausea
- c Cold pressor test¹⁸
 - (1) Indication—to determine response of blood pressure and vasomotor irritability to cold
 - (2) Method
 - (a) Subject should rest for 20 min (omit sedation)
 - (b) Blood pressure is taken every 5 min until a constant level is reached
 - (c) One hand is immersed (above wrist) into ice water for 1 min blood pressure (using opposite arm) read at 30, 60 and every 120 sec until highest level obtained

(3) Results

- (a) Normal—minimal response (rarely rise of 10 mm mercury) in systolic and diastolic pressure to local cold stimuli
- (b) Pheochromocytoma—response may be
 - [1] Normal
 - [2] Hypertensive
- (c) Hypertension (organic forms)
 - [1] Systolic and diastolic pressures rise
 - [2] Delay in return of blood pressure to basal level
- 5 Roentgenographic findings
 - a Chest—for intrathoracic tumor²²
 - b Air insufflation is advisable, if necessary, presacral technic⁶
 - c Pyelogram for
 - (1) Adrenal tumor
 - (2) Kidney displacement

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FIG 263 ADRENAL GLAND Normal adult adrenal gland The different zones are not well demarcated Zona fasciculata is easily recognized by the longitudinal arrangement of darker staining cells Zona reticularis and medulla fuse into one another ($\times 29$)

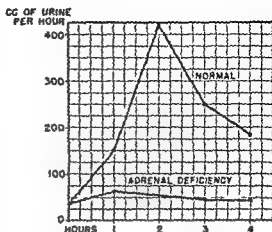


CHART 87 ADRENAL WATER TEST The chart illustrates diuresis in a normal individual (peaked curve) after ingestion of water as compared with water retention in a case of Addison's disease (flat curve) Nine cc of water/1 lb of body weight was given 1 hr before first specimen was collected

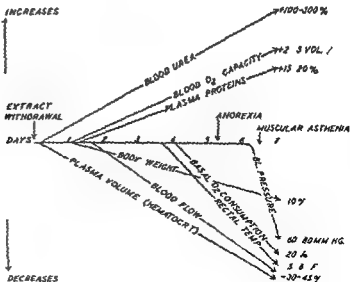


CHART 86 PHYSIOLOGIC CHANGES FOLLOWING WITHDRAWAL OF ADRENOCORTICAL EXTRACT IN ADRENALECTOMIZED ANIMALS (Turner C D General Endocrinology (modified from Loeb R F Glandular Physiology and Therapy) Philadelphia Saunders p 228)

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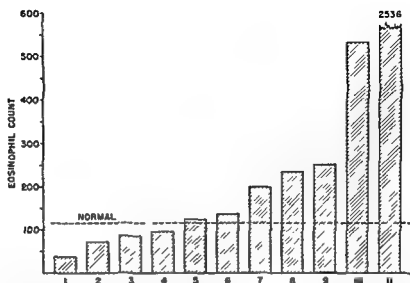


CHART 89 TOTAL EOSINOPHIL COUNTS IN VARIOUS ENDOCRINOLOGIC AND SYSTEMIC DISORDERS. The broken line is the average of 180 separate total eosinophil counts taken on different blood samples from 16 normal females

NO	TYPES OF CASES	CASES	RANGE
1	Cushing's syndrome	4	0-100
2	Hirsutism obesity abdominal striae hypertension or mild virilism	18	0-14
3	Gonadal disturbances		
	Ovarian agenesis	4	38-250
	Hypergonadotropic type with tubular failure	1	
	Precocious puberty	1	
4	Enlarged sella turcica	7	0-181
5	Acromegaly	4	18-187
6	Myxedema	4	20-250
7	Addison's disease	1	260
8	Pituitary insufficiency		182-462
	Simmonds type	3	
	Sheehan's type	2	
9	Rheumatoid arthritis	8	68-681
10	Hypopituitary conditions		400-688
	Pituitary dwarf	2	
	Postoperative pituitary tumor	2	
11	Atopic dermatitis	2	1919-4731

The average for these was 2536 and is included to show high total eosinophil count in a disease in which eosinophilia is a characteristic finding

A larger experience has demonstrated that the level of circulating eosinophils is diagnostically unreliable in any one case

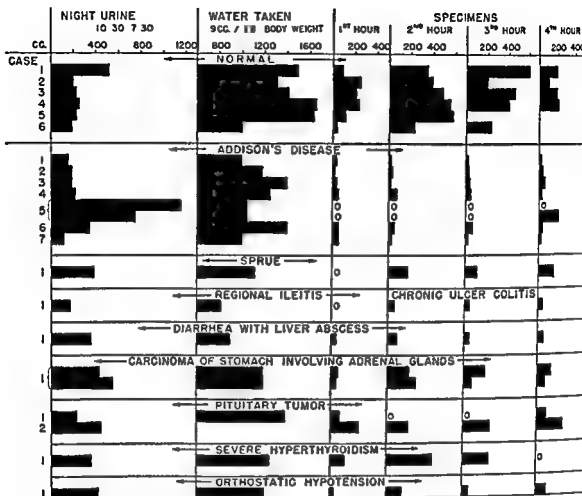


CHART 88 ADRENAL WATER IN VARIOUS DISEASES Part I of the test and the water excretion each hour after ingestion of water (Bartels)

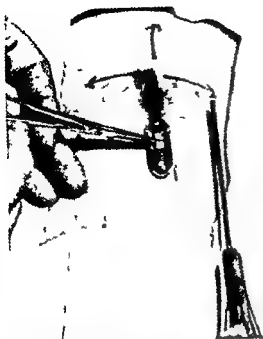


FIG 269 PELLET IMPLANTATION WITH TROCAR. The pellet is being inserted. The rod by which it is pushed in is shown at right. The arrows indicate the direction in which other pellets are to be implanted.

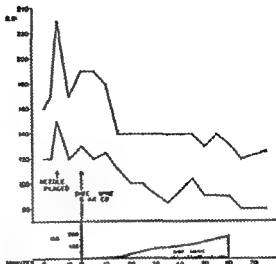


CHART 92 DIBENAMINE TEST IN PHEOCHROMOCYTOMA. Dibenamine was cautiously introduced in the vein. B.P. fell to a level lower than has been noted previously due to persistent hypertension (see also Chart 91) (Bartels E. C. and Cattell T. Pheochromocytoma: its diagnosis and treatment. Ann. Surg. 131: 903-916).

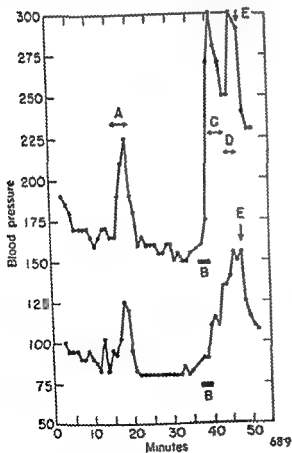


CHART 93 SEVERE REACTION TO BENZODIOXANE IN HYPERTENSION. (A) Spontaneous rise in B.P. producing precordial pain. (B) Injection of benzodioxane by rise in blood pressure, light headedness, vertigo and severe precordial pain. (Drill V. A. Reactions from use of benzodioxane (933 F) in diagnosis of pheochromocytoma. New England J. Med. 241: 777-789).

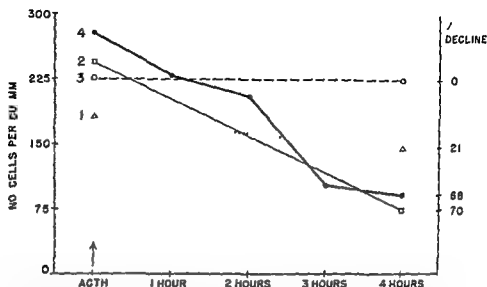


CHART 90 TOTAL CIRCULATING EOSINOPHILS PER CU MM BEFORE AND AFTER INTRAMUSCULAR INJECTION OF ACTH (1) Age 30 normal male Without injection of ACTH (not fasting on first count) (2) Normal obese young woman after injection of 30 mg of ACTH A normal response is shown by a 70% decline in total eosinophilic count (3) Counts on blood withdrawn before injection of ACTH and again after 4 hrs incubation (Patient 2) Note no change in count (4) Age 28 male with Reiter's syndrome Results after 60 mg of ACTH Normal response 68% decline in the total number of eosinophils

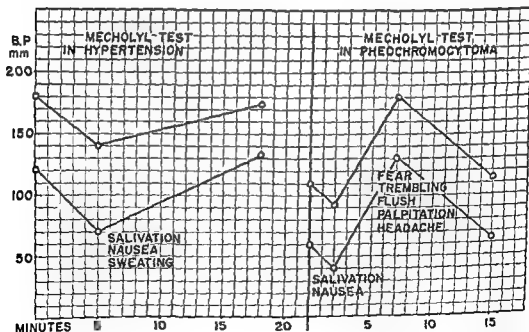


CHART 91 MECHOLYL TEST The chart shows the effect of mecholyl on BP in a hypertensive patient as compared with one with pheochromocytoma. In the cases tested so far the injection of mecholyl has been followed by a rise in pressure as illustrated. A similar provocative action may be obtained by the use of histamine and tetraethylammonium bromide. Negative responses do not always exclude pheochromocytoma (Guarnieri V and Evans J A Pheochromocytoma report of case with new diagnostic test Am J Med 4 806 813)

	face Lauckles nipples axillae, penis, scrotum labia anal region bluish black freckles are very characteristic all mucous membranes and ocular fundi may show patchy bluish black discolorations nails may have pigment spots or longitudinal bands ⁹⁴ vitiligo present in 1 to 20 per cent ¹⁰⁰ reported in Negroes (see Figs 271 273, 275) ⁹⁰ Over 98 per cent of cases have bronzing of the skin
■ Color	
2 Hair	
a Head	Normal
b Facial	Normal
c Axillary	Regrows slowly after shaving occasionally absent
d Pubic	Normal decreased or, rarely absent (see Fig 274)
e Body	Normal
F HEAD	
1 Shape and size	Normal
2 Facial expression	Often languid listless dull
3 Eyes	
a General	Normal conjunctivae and sclerae may be pigmented
b Fundi	Normal or may show pigment
c Visual	
(1) Fields	Normal
(2) Acuity	Normal
4 Ears and nose	Normal hearing may be decreased
5 Mouth and throat	
a General	Not remarkable bluish black pigmentation of mucous membranes and tongue
b Teeth	Normal tend to have apical abscesses and poor gums
c Larynx (voice)	May be weak on account of general muscular atonia
G NECK	
1 General	Normal typical pigmentation may be found
2 Thyroid	Normal
H CHEST	Normal or signs of healed or active tuberculosis
I HEART AND PERIPHERAL VESSELS	
1 Heart	Small sounds may be faint and distant
2 Rate and rhythm	Normal or tachycardia
3 Blood pressure	Depends on level before onset of disease but usually reduced low or unobtainable in acute crisis average systolic 80 to 100 mm and diastolic 50 to 70 mm ¹⁰
4 Peripheral arteries and veins	Soft thin or not palpable erect posture may aggravate hypotension and increase pulse rate resulting in syncope (see 40 XIV F)
5 Vasomotor	Loss of tone presumably no flushing
J BREASTS	
1 Male	Normal occasionally gynecomastia ^{6, 77} increased pigmentation of areolae
2 Female	Loss of fat areolae are darker than normal
K ABDOMEN	
1 Liver	Normal
2 Spleen	May be palpable
3 Hernia	None
4 Tumor	None as a rule

SECTION 40

ADDISON'S DISEASE

- I DEFINITION** A condition resulting from almost complete destruction of the adrenal cortices and characterized in general by asthenia, weight loss, low blood pressure, gastro intestinal symptoms and often pigmentation of skin and mucous membranes, acute or chronic types may occur
- II APPEARANCE** Thin, often with localized areas of pigmentation and lacking the bloom of health, severe or acute cases look very ill, languorous and their prostration may be quite marked (see Figs 270 and 271)
- III AGE** Any age, chiefly 20 to 40 years, youngest reported at 6½ months^{10-18 104 105}
- IV SEX** About equal, slight male predominance¹⁰²
- V MENTAL DEVIATIONS**
- A INTELLIGENCE** Normal variations
- B RESPONSIVENESS** May be impaired because of exhausting nature of disease
- C OTHER ABNORMALITIES** Irritability depression, delirium, coma
- VI PHYSICAL STATUS**
- A NUTRITION** Rarely cachexia
- 1 Weight** Below average all lose some—about 20 or 30 lbs is common
- 2 Fat distribution** Little or no fat deposits
- II STATURE** Normal even when disease develops in childhood decreased height age¹⁰⁴
- C EXTREMITIES**
- 1 Upper** Normal elbows may have a grayish silver appearance
- a Hands** Normal
- b Fingers** Normal knuckles, nail beds and creases of palms may be pigmented
- c Span** Normal
- 2 Lower** Normal knees may be pigmented
- a Feet** Normal
- b Toes** Normal
- D SPINE** Normal
- E INTEGUMENT**
- 1 General** Maintains elasticity normal amount of moisture but changes in electrolytic content (see 40 VI D)
- a Texture** Normal desquamation has been reported
- b Temperature** Subnormal if no infection may be elevated with carcinoma of adrenals¹⁸
- c Eruptions** None
- d Pigmentation** No change or else various shades of darkening, from light tan to burnt umber most prominent in exposed areas, scars or parts subjected to friction, as elbows neck,

4	Uric acid	Normal or increased in crisis
5	Cholesterol	Variable usually low
6	Sodium	Variable depending on chloride level decreased in crisis
7	Potassium	Normal or increased in crisis
8	Calcium	Normal or increased ^{18 41 60}
9	Phosphorus	Normal or slightly increased ^{18 41 60}
10	Phosphatase	Normal
11	Chlorides	Variable, depending on sodium level but may be independent of potassium values usually decreased in crisis ⁷
12	Iodine	Normal ¹
13	Creatine	Normal or increased ⁶²
14	Magnesium	Normal ¹⁸ or increased ⁶⁰
15	Bilirubin	Normal ¹⁰¹
16	Bicarbonate	Normal may go down with chlorides during crisis
17	Carbon dioxide combining power	Normal or decreased ^{60 61}
18	Vitamin C	Low ⁶¹
D FUNCTION TESTS		
1	Tolerance	
a	Glucose	
(1)	Oral	Low curve with venous blood normal curve with capillary blood, if absorption is adequate (see Table 102, p 1426 103 III 3 a) ⁶⁸
(2)	Intravenous	Normal curve ⁹
b	Glucose insulin	Flat curve
c	Insulin	Normal or marked prolongation of hypoglycemic response
2	Adrenal water	Positive ⁷
3	Salt deprivation	Positive ⁷
4	Balance	
a	Nitrogen	Negative often
5	Renal	
a	Phenolsulfonphthalein	Normal or decreased ⁶⁶
b	Clearance	
(1)	Urea	Normal or decreased
(2)	Creatinine	Decreased ⁶¹
(3)	Inulin	Decreased ⁶⁰
6	Liver	
a	Bromosulphthalein	Impaired
b	Hippuric acid (IV)	Below normal ¹⁰⁰
7	ACTH	Positive (see 39 VIII A 5 c) ^{45 60 70 124}
E MISCELLANEOUS TESTS		
1	Basal metabolic rate	Moderately low average minus 15 to minus 20 per cent ^{5 4}
2	Circulation time	No data probably decreased
3	Sedimentation rate	Increased usually
4	Specific dynamic action of protein	No data
5	Gastric analysis	Achlorhydria common free hydrochloric acid is reduced
6	Electrocardiogram	No typical changes ^{11 39 101 1} low isoelectric or diaphasic T waves in all leads T ₁ T ₂ inverted occasionally and T ₃ T ₄ frequently ST interval may be prolonged

L GENITALIA**1 Male**

- a Penis Normal, may be pigmented
- b Testes Normal
- Prostate Normal or atrophied⁶⁷

2 Female

- a External Normal, outer margin of labia may be pigmented
- b Internal Normal

M NEUROMUSCULAR

- 1 Muscles Weakness, loss of tone
- 2 Gait As might be expected with varying degree of weakness
- 3 Body movements Not remarkable, other than listless
- 4 Tremor None
- 5 Paresthesias None
- 6 Reflexes Normal

N SPEECH

As with severe asthenia, occasionally slurred

VII LABORATORY DATA**A URINE**

- 1 General Decreased output specific gravity often high, other changes due to local kidney disease as tuberculosis, pyelonephritis or nephrosis
- 2 Special analyses
 - a Sugar Absent or present only with associated diabetes mellitus
 - b Albumin May be found
 - c Nitrogen Normal
 - d Creatine Normal or increased⁶⁸
 - e Creatinine Normal
 - f Sodium Increased until body depletion occurs
 - g Potassium Decreased
 - h Calcium Normal
 - i Phosphorus Normal
 - j Chlorides Increased until body depletion occurs
 - k Iodine Normal

B HEMATOLOGY⁹

- 1 Red blood cells Decreased slightly (rarely below 3 million) or increased with hemoconcentration
- 2 Hemoglobin Decreased or increased with hemoconcentration
- 3 White blood cells Normal or slightly below, little rise with infection¹¹
- 4 Differential Relative lymphocytosis except with infection when percentage may drop eosinophils (total) average 322/cu mm¹¹²
- 5 Hematocrit Normal or increased during crisis

C BLOOD CHEMICAL ANALYSES (abnormal changes develop chiefly during a crisis or impending crisis)

- 1 Sugar Normal or low (true diabetes may be present)^{11 98}
- 2 Nonprotein nitrogen Normal or increased⁹
- 3 Protein
 - a Albumin Normal or increased with hemoconcentration in crisis
 - b Globulin Normal or decreased^{123 41 65}
 - A/G ratio Normal or increased^{3 41 65}
 - d Fibrinogen Normal or decreased^{16 41 65}

IX ETIOLOGY

A. PRIMARY CAUSES^{34, 122}

- 1 Tuberculosis (69.7%) (seldom primary)

TABLE 50 RELATION TO TUBERCULOSIS*

	NUMBER OF CASES
Previous history of tuberculosis with recovery	31
Tuberculosis (till active) before onset of Addison's disease	26
No history of tuberculosis	27

* Lungs, bones, glands, kidneys

TABLE 51 CLINICAL EVIDENCE OF TUBERCULOSIS ELSEWHERE

	NUMBER OF CASES
Pulmonary	60
No evidence	31
Questionable	10
Elsewhere	
Bone	34
Lymph nodes etc	7
Genito-urinary tract	4
Gastro-intestinal tract	1

TABLE 52 FIFTY-ONE CASES WITH TUBERCULOSIS OF ADRENALS

INVOLVEMENT	FINDINGS	NUMBER OF CASES
Unilateral	No symptoms	15*
Bilateral	Clinical signs	25
Bilateral	Latent	6
Bilateral	Undiagnosed	5

* It is probable that evidence of adrenal insufficiency might be obtained in more of these cases today

- 2 Idiopathic atrophy (16.1%) — Many factors have been considered as acute or chronic diseases but cause still remains obscure
- 3 Amyloid disease (1.7%)
- 4 Hemochromatosis
- 5 Tumor (1.7%) (see Protocol 40 XXXI)
 - a Malignant destruction
 - b Pressure atrophy
- 6 Venous thrombosis (0.7%)
- 7 Embolism (0.2%)
- 8 Syphilis (0.2%)
- 9 Pituitary hypofunction (see 7)

- 10 Removal of adrenal tumor with absent or atrophic gland on other side
- 11 Torulosis or histoplasmosis⁷
- 12 Scleroderma
- 13 Meningococcus—see 41 III & 2108

B. SECONDARY CAUSES

- 1 Pheochromocytoma
- 2 Carcinoma of cortex
- 3 Metastatic cancer especially of lungs⁹
- 4 Removal of sufficient adrenal tissue

X PATHOLOGY

A. Gross

- 1 Adrenal glands^{1, 9, 28, 36, 171 & 102}
 - a Atrophy—primary contracted adrenal (3 of 19 autopsied cases at Lahey Clinic)
 - (1) Size
 - (a) Very small, difficult to find
 - (b) Weight—0.75 to 3 Gm
 - (2) Color—gray to brownish red
 - (3) Surface—smooth often resembling cirrhotic liver
 - (4) Cortex—thin
 - (5) Medulla
 - (a) Normal
 - (b) Reduced
 - (6) Both glands involved
 - b Hypoplasia—small size
 - c Tuberculosis (15 of 19 autopsied cases at Lahey Clinic or 79%)
 - (1) Size—often enlarged, about 22 to 28 Gm
 - (2) Color
 - (a) Yellow
 - (b) Yellowish gray
 - (c) Reddish gray
 - (3) Capsule
 - (a) Thickened
 - (b) Adherent
 - (4) Consistency—rubbery
 - (5) Cortex and medulla may be destroyed
 - (a) Completely
 - (b) Partially
 - (6) Caseation with abscess (see Fig 277)
 - (7) Calcified areas
 - (8) Hemorrhage
 - (9) Process may be
 - (a) Acute
 - (b) Chronic
 - (c) Combination of both

	<i>low complexes, pattern may revert to normal or further signs of myocardial damage may develop, due to an increase in heart size with therapy⁴³</i>
7 Blood volume	Normal or decreased in crisis
8 pH	No data
9 Total base	Normal or decreased in crisis
10 Spinal fluid	No data
11 Fecal excretion	No data
12 Electro encephalogram	Slower alpha rhythm and frontal preponderance than normal, absence or decreased number of low voltage, fast frequency (beta) waves, sensitivity to hyperventilation is increased, about 70 per cent have abnormal findings ⁴³
F URINARY HORMONE ASSAYS	
1 FSH	Normal ^{7 84 64 67 87}
2 LH	No data
3 Estrogens	Normal (also in pregnancy) ^{64 7, 87}
4 Pregnanediol	May be present premenstrually or continuously if DOCA is administered normal in pregnancy ^{4 87}
5 17 ketosteroids	Low, about 1 to 4 mg/24 hrs in females about 1 to 9 mg/24 hrs in males ^{11 7 44 62 67 8, 87 100 13 134}
6 11 oxysteroids	Low or absent ^{22 31 10 131 13}
7 Aschheim Zondek	No data
8 TSH	No data
G BIOPSY	
1 Endometrial	Normal, if regular catamenia
2 Testicular	Atrophic changes possible, but usually normal ⁷⁹ ■
H VAGINAL SMEAR	
	Normal
I SEMEN ANALYSIS	
	Normal
VIII ROENTGENOGRAPHIC FINDINGS	
A SKULL	
1 Cranial vault	Normal
2 Sella turcica	Normal
3 Sinuses	Normal
4 Mandible	Normal
5 Teeth	Normal, apical abscesses are common
B EPIPHYSEAL STATUS (bone age)	
	No retardation reported in children but the number of cases is too small for any definite conclusion ¹⁰⁴
C LONG BONES	
	Normal
D VERTEBRAE	
	Normal
E BONE TEXTURE	
	Normal possibly osteoporosis if disease is of a long duration
F MISCELLANEOUS	
1 Chest	Normal, active or healed tuberculosis heart size below the normal except when complicated with cardiac disease (see Fig 276) ¹¹⁰
2 Flat plate of abdomen	Positive signs of adrenal calcification may be found (31.5% of cases) ⁸⁸ or tumor

IX ETIOLOGY

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- 11 Torulosis or histoplasmosis⁷⁹
- 12 Scleroderma
- 13 Meningococcus—see 41 III A 2¹⁰⁶

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- 1 Pheochromocytoma
- 2 Carcinoma of cortex
- 3 Metastatic cancer, especially of lungs⁹
- 4 Removal of sufficient adrenal tissue

X PATHOLOGY

1 GROSS

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- a Atrophy—primary contracted adrenal (3 of 19 autopsied cases at Lahey Clinic)

(1) Size

- (a) Very small difficult to find
- (b) Weight—0.75 to 3 Gm

(2) Color—gray to brownish red

- (3) Surface—smooth, often resembling cirrhotic liver

(4) Cortex—thin

(5) Medulla

- (a) Normal
- (b) Reduced

(6) Both glands involved

- b Hypoplasia—small size

- c Tuberculosis (15 of 19 autopsied cases at Lahey Clinic or 79%)

- (1) Size—often enlarged, about 22 to 28 Gm

(2) Color

- (a) Yellow
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- (c) Reddish gray

(3) Capsule

- (a) Thickened
- (b) Adherent

(4) Consistency—rubbery

- (5) Cortex and medulla may be destroyed

- (a) Completely
- (b) Partially

- (6) Caseation with abscess (see Fig 277)

(7) Calcified areas

(8) Hemorrhage

- (9) Process may be

- (a) Acute
- (b) Chronic
- (c) Combination of both

- (10) Never healed³⁶
- (11) Total destruction³⁶
 - (a) Both \pm 80 per cent
 - (b) One and other incompletely \pm 20 per cent
- d Tumors
 - (1) Benign
 - (a) Encapsulated usually
 - (b) Cause pressure in
 - {1} Medulla
 - {2} Cortex
 - (2) Malignant
 - (a) Destructive
 - (b) Invasive
 - (c) Bilateral often, if metastatic or primary
- e Blood vessel disorders
 - (1) Emboli
 - (a) Flea bitten appearance, if multiple infected areas
 - (b) Gross infarction
 - (2) Thrombosis of adrenal veins
 - (a) Gross hemorrhagic diathesis
 - (b) Glands are
 - {1} Enlarged
 - {2} Dark red color
- f Amyloidosis
 - (1) Size
 - (a) Normal
 - (b) Increased slightly
 - (2) Color
 - (a) Gray
 - (b) Yellow
 - (3) Capsule—smooth
 - (4) Consistency—firm
 - (5) Zones well preserved
- g Hemochromatosis—cortex of adrenal contains excessive iron pigment
- h Various causes producing hemorrhage and altered conditions (gross appearance variable)
 - (1) Monilia
 - (2) Leukemia
 - (3) Syphilis
 - (4) Acute febrile disease
 - (5) Chemical poisoning
 - (6) Injury or wounds
 - (7) Meningococcus
 - (8) Typhus
- 2 Pituitary
 - a Atrophy may occur with tuberculosis of adrenals³⁰
 - b Capillary dilatation
- 3 Thyroid often shows lymphocytic infiltration³⁶
- 4 Ovaries and testes rarely affected³⁶
- 5 Lymphoid tissue
 - a Generalized hyperplasia
 - b Thymus reported enlarged in a few cases but evidence is not conclusive^{36 75}
 - c Spleen may be larger than normal in some cases³⁶
- 6 Gastro intestinal tract
 - a Ulcerations (small punched out areas) of
 - (1) Stomach
 - (2) Duodenum
 - (3) Jejunum
 - b True peptic ulcer in 22 per cent of autopsied cases³⁶
 - c Tuberculosis
- 7 Heart
 - a Color—brownish
 - b Size
 - (1) Normal
 - (2) Small usually
- 8 Lungs
 - a Normal
 - b Tuberculosis
 - (1) Healed
 - (2) Active
- 9 Other organs—tuberculosis may be found
 - a In most any organ
 - b Everywhere from miliary spread
- B Microscopic
 - 1 Adrenals^{1 9 25 36 38 39}
 - a Atrophy—'primary contracted adrenal'
 - (1) Loss or destruction of cortical cells
 - (2) Round cell infiltration of cortex
 - (3) Medulla may be spared
 - (4) Sclerosis
 - b Hypoplasia
 - (1) Cortex—decreased
 - (2) Medulla—normal
 - c Tuberculosis
 - (1) Medulla practically always involved
 - (2) Tubercles and tubercle bacilli are abundant
 - (3) Caseation with abscess
 - (4) Hyperplasia or small cortical adenomas

- (5) Hemorrhagic areas
- (6) Tuberculosis is never completely healed
- d Amyloidosis—particularly involves capillaries of cortex
- e Tumors of cortex—see 42 IX B
- f Hemochromatosis—excessive deposition of
 - (1) Hemosiderin
 - (2) Hemofuscin
- g Blood vessel abnormalities
- 2 Pituitary—see 2 IX B 16
- 3 Lymphoid hyperplasia and infiltration of many organs
- 4 Heart—lysis of muscle fibers

XI PATHOLOGIC PHYSIOLOGY

A INTRODUCTION—Almost complete destruction or functional loss of both adrenal cortices is necessary to produce clinical signs or symptoms of adrenal insufficiency

B CARBOHYDRATE METABOLISM

- 1 Deficiency of sugar (S) hormones may be postulated
 - a Carbohydrate utilization is not impaired but possibly increased thus favoring hypoglycemia
 - b The immediate expenditure of amino acids for energy leads to
 - (1) Depletion of glycogen stores in
 - (a) Muscles
 - (b) Liver
 - (2) Hypoglycemia
 - c Failure to convert amino acids derived from protein and fat into liver glycogen⁴⁹
 - d Gastrointestinal effects
 - (1) Absorption of sugar is probably decreased
 - (2) Glucose tolerance curves
 - (a) Oral—flat type
 - (b) Intravenous—normal but severe hypoglycemic reactions may occur several hours later
 - e Insulin sensitivity is increased

C PROTEIN METABOLISM

- 1 Deficiency in nitrogen retaining and tissue synthesizing hormones may ensue
- 2 Essential amino acids may be used immediately for energy purposes (see above) thus denying these building

blocks for new tissue synthesis (or replacement)

- 3 A negative nitrogen balance is the eventual outcome

D SODIUM AND POTASSIUM METABOLISM

- 1 Deficiency in electrolytic hormones of adrenal cortex
- 2 Failure to conserve sodium and chloride, by loss through the renal tubules and sweat glands results in
 - a Withdrawal of fluid from intra cellular spaces
 - b Decreased plasma volume due to redistribution of water
- 3 A decrease in urinary excretion of water and sweating occurs apparently in an attempt to save these electrolytes (see Table 53)
 - a When this measure fails a low blood sodium and chloride may be found
 - b This is the primary effect after adrenalectomy in animals⁵⁰
 - c Posterior pituitary antidiuretic substance may be increased⁵¹
- 4 Sodium and chloride are poorly absorbed by intestines further complicating the whole process
- 5 Retention of potassium due to a low urinary output leads to an increased concentration in the
 - a Blood
 - b Erythrocytes
 - c Skeletal muscle

E RESPIRATORY METABOLISM

- 1 Lowered metabolic rate including decreased tissue activity is not mediated through pituitary or adrenals
- 2 Respiratory quotient is elevated in patient with carbohydrate metabolic defects⁵²⁹
- 3 Deficiency in various hormones especially epinephrine is basic factor

F CARDIOVASCULAR SYSTEM

- 1 Low blood pressure is not due entirely to loss of epinephrine but probably to deficient steroids as well
- 2 Sodium and weight loss favor hypotension

G DERMATOLOGIC METABOLISM

- 1 Mechanism of skin changes is not known
- 2 Findings are caused perhaps by an excess of an intermediary compound

which is normally synthesized into epinephrine¹³

- 3 Pigmentation occurs in areas of
 - a Pressure
 - b Exposure to light
 - c Injury
- 4 Electrolytic composition of sweat (thermal) parallels the composition of urine, there is an increase of
 - a Sodium
 - b Chloride

TABLE 53 SWEAT TESTS¹⁰

	CHLORIDE CONCENTRATIONS IN MEQ/L
Normal range	17.5 to 58.0
Adrenal cortical carcinoma with Cushing's syndrome	1.7 and 2.7
Adrenal cortical carcinoma with adrenogenital syn- drome	5.7 and 9.1
Cushing's syndrome with out carcinoma (2 cases)	5.9 to 13.5
Panhypopituitarism (3 cases)	68.0 to 75.0
Addison's disease (7 cases)	
Untreated	105.0 to 122.0
Treated	25.0 to 63.0

H ADAPTABILITY TO SHOCKING STIMULI

- 1 Sudden death in Addison's disease is often unexplained
- 2 Adrenalectomized animals are very sensitive to shocking stimuli
- 3 Loss of adrenocortical function should prevent the establishment of a counter shock phase in the alarm reaction (Selye) (see 99 II A 5)
- 4 Thymus and lymphoid involution and release of immune globulins may not occur
- 5 Hypoglycemia becomes severer because of failure to release adrenocortical carbohydrate hormones

I URINARY HORMONE ASSAYS

- 1 FSH—not increased
- 2 17 ketosteroids
 - a Absent in females
 - b Decreased in males
- 3 11 oxysteroids
 - a Absent
 - b Decreased

J SUMMARY

- 1 Apparently none of these altered func-

tions is the complete cause of adrenal insufficiency in animals or man

- 2 It is unlikely that these changes are entirely independent, but rather overlap in significant degrees
- 3 While desoxycorticosterone is thought to effect only sodium and potassium, the clinical improvement with this synthetic compound would indicate some action on sugar and protein metabolism^{45 135}
 - a There is also evidence that it prevents depletion of fat stores in the adrenalectomized animal
 - b An increase in appetite may account for
 - (1) Greater protein intake
 - (2) Weight gain

XII SYMPTOMATOLOGY

A ACUTE (including adrenal crisis)

- 1 Onset may be sudden from
 - a An acute process as
 - (1) Infection
 - (2) Necrosis
 - b Exacerbation of an unsuspected or known chronic adrenal insufficiency case due to
 - (1) Above factors
 - (2) Salt restriction
 - (3) Hemorrhage
 - (4) Trauma
 - (5) Surgery
- 2 Fever (if acute infection)
- 3 Prostration
- 4 Abdominal pain, may be severe
- 5 Vomiting
- 6 Diarrhea
- 7 Hiccough
- 8 Tachycardia
- 9 Blood pressure, low
- 10 Anuria
- 11 Hypothermia
- 12 Sudden collapse (shock)
- 13 Coma

II CHRONIC

- 1 Gradual onset of asthenia
- 2 Neuromuscular and sensory
 - a Weakness
 - (1) With effort
 - (2) At rest
 - (3) On speaking
 - b Dimming of vision

- c. Giddiness
- d. Vertigo
- e. Tinnitus
- f. Syncope
- g. Apathy
- h. Mental
 - (1) Depression
 - (2) Sluggishness
 - (3) Hallucinations
 - (4) Delusions
- i. Headache (rare)
- j. Irritability
- k. Convulsions and other symptoms due to hypoglycemia (see 85 \II)
- l. Muscular and joint pains and stiffness, may have associated rheumatoid arthritis
- m. Cold extremities
- J Cardiorespiratory
 - a. Few symptoms only
 - b. Breathlessness occasionally
 - c. Palpitation
- 4 Gastro-intestinal
 - a. Anorexia aversion to all foods
 - b. Nausea
 - c. Hiccough
 - d. Vomiting
 - e. Diarrhea
 - (1) Constant
 - (2) Intermittent
 - (3) Common during crisis
 - f. Constipation
 - g. Abdominal discomfort or pain
 - (1) Mild
 - (2) Severe
 - h. Hemorrhage may occur
- 5 Genito-urinary
 - a. Males
 - (1) Loss of libido
 - (2) Impotence
 - b. Females
 - (1) Menstrual cycle remains normal in most cases - ⁶⁰ ₇₂
 - (2) Pregnancy may occur⁵⁴ ₅₇
 - (3) Lactation is impossible
- b. Nausea vomiting and diarrhea may be present
- 2 Weakness and easy fatigability which are not complained of with a smile (patient's behavior consistent)
- 3 History of
 - a. Unconsciousness
 - b. Faintness
 - c. Convulsions with hypoglycemia
- 4 Bronze pigmentation on exposed areas of friction or black freckles on mucous membranes without any other symptoms do not always mean adrenal insufficiency
- 5 Normal or low blood pressure, if not found and other evidence is impressive inquire as to previous hypertension
- 6 Laboratory evidence
 - a. Decrease during crisis of
 - (1) Sugar (fasting)
 - (2) Sodium (serum)
 - (3) Chlorides (serum)
 - (4) Plasma volume
 - b. Increase (normal with hemoconcentration) during crisis
 - (1) Sodium (urinary)
 - (2) Chlorides (urinary)
 - (3) Hematocrit
 - (4) Nonprotein nitrogen (blood)
 - (5) Urea (blood)
 - (6) Protein (serum)
 - (7) Potassium (serum)
 - c. Water test—positive
- 7 Roentgenographic evidence of adrenal calcification in some cases (16%)
- 8 Provocative tests
 - a. Sodium deprivation (see 39 \III A 5 d)
 - (1) This is not recommended except in unusual cases
 - (2) The water test if positive in Part I and II is just as reliable supportive evidence and not fraught with danger
 - b. Adrenocorticotrophic hormone test (Thorn)⁴ (see 39 \III A 5 c)
 - (1) Eosinophils show little or no drop in count
 - (2) Uric acid excretion is increased less than 50 per cent of normal
 - c. Epinephrine test—eosinophils show little or no change in count (see 39 \III A 5 b)⁵⁰

XIII DIAGNOSIS

A GENERAL SUMMARY

- I Unexplained gastro intestinal disturbances
 - a. Abdominal pain associated with
 - (1) Anorexia
 - (2) Weight loss

XIV DIFFERENTIAL DIAGNOSIS

A CONDITIONS WITH PIGMENTATION OF SKIN AND/OR MUCOUS MEMBRANES

- 1 Hemochromatosis
 - a It may be associated with adrenal insufficiency⁴⁵
 - b Mucous membranes are not pigmented
 - c Black freckles—absent
 - d Skin—bronze
 - e Enlargement of
 - (1) Liver
 - (2) Spleen
 - f Ascites—late in disease
 - g Glycosuria—often
 - h Hyperglycemia
 - i Positive test for iron in
 - (1) Skin biopsy
 - (2) Urinary cellular elements
- 2 Hyperthyroidism (see 26 XIII)
 - a Appetite—good
 - b Mucous membranes are not affected
 - c Black freckles—absent
 - d Skin pigmentation is increased, partly from weight loss; vitiligo is more common
 - e Thyroid—enlarged
 - f Tremor—fine
 - g Basal metabolic rate—increased
- 3 Myxedema (see 25 XIII)
 - a Skin
 - (1) Dry
 - (2) Thick
 - (3) Black freckles—absent
 - (4) Pigmentation
 - (a) Patchy
 - (b) Cafe au lait
 - b Cholesterol (plasma)—high
 - c Basal metabolic rate—usually much lower
- 4 Pellagra
 - a Pigmentation on exposed surfaces mostly hands and wrists
 - b Concomitant dermatitis—common
 - c Tongue—beefy red
 - d Delirium
 - e Diarrhea persists

NOTE The following can be easily eliminated by history and no signs, symptoms or laboratory findings of Addison's disease

- 5 Argyria
 - a History of using nose drops or other preparations containing silver

- b Mucous membranes are not involved
- c Black freckles—absent
- d Skin color
 - (1) Bluish
 - (2) Silver gray
- e Nails affected
- 6 Vitiligo
 - a Normal health
 - b Mucous membranes are not affected
- 7 Chloasma (liver spots)—small, brown pigmented areas
- 8 Internal medications
 - a Phenolphthalein
 - b Arsenic
 - c Bismuth—typical line on gums in some cases
- 9 Pigmentation from external causes
 - a Sunburn
 - b Heat
 - c Irradiation (also atomic bomb)
 - d Local application of
 - (1) Lead
 - (2) Mercury
 - (3) Any skin irritant
- 10 Racial groups
 - a The following have skin pigmentation similar to Addison's disease
 - (1) Ethiopians
 - (2) Orientals
 - (3) Latins
 - (4) Levantines
 - (5) American Indians
 - b Black freckles—absent
- 11 Acanthosis nigricans
 - a Intra abdominal mass
 - b Evidence of malignant metastases
 - c Cutaneous biopsy is diagnostic

B CHRONIC NERVOUS EXHAUSTION CONSTITUTIONAL INADEQUACY AND PSYCHASTHENIA

- 1 Long history consistent with above
- 2 Weight loss is not significant
- 3 Pigmentation if present is not characteristic
- 4 Good one day bad the next
- 5 Water test—normal in majority
- 6 ACTH test—normal
- 7 17 Ketosteroids—normal

C ANOREXIA NERVOSA

- 1 Females affected more often than in Addison's disease
- 2 Amenorrhea—more frequent
- 3 Weight—loss usually without diarrhea

- 4 Mucous membranes—normal
 - 5 Black freckles—absent
 - 6 Water test—may be positive
 - 7 ACTH test—normal
 - 8 17 ketosteroids—may be low
 - 9 Slight change with therapeutic use of
 - a Salt
 - b Glucose
 - c Desoxycorticosterone
 - 10 Improvement with adequate nutrition (voluntary or forced) (see 5 XIV A 106 III E)
- D CONVALESCENT STATES FROM INJURY IN FECTIONS AND OPERATIONS** (see Adaptation syndrome 99)
- E HYPOPITUITARISM**
- 1 All or many signs and symptoms of primary adrenal insufficiency
 - 2 Notably absent or rare
 - a Diarrhea
 - b Weight loss which is
 - (1) Great
 - (2) Rapid
 - c Pigmentation
 - d Sexual hair
 - e Sexual function
 - 3 Sella turcica may be enlarged
- F POSTURAL HYPOTENSION (idiopathic)^a**
- 1 Pulse rate does not rise with a fall in blood pressure when standing
 - 2 Effect is not through epinephrine for medulla is intact¹⁰
- G HYPERINSULINISM**
- 1 Hypoglycemic symptoms occur at a blood sugar level of 50 mg % instead of 60 mg %¹¹¹
 - 2 No physical signs of adrenal insufficiency
- H DISEASES IN WHICH POSITIVE WATER TEST MAY BE PRESENT WITHOUT OTHER EVIDENCE OF ADRENAL INSUFFICIENCY**—see 39 XIII A 5 a (6) (7) ¹
- I SALT LOSING NEPHRITIS^{1,8}**
- 1 Nonprotein nitrogen—elevated
 - 2 Carbon dioxide combining power—low
 - 3 Renal function—poor
 - 4 Failure to respond to desoxycorticosterone but possibly to cortisone
 - 5 Sodium chloride therapy—effective
- J DISORDERS ASSOCIATED WITH SODIUM LOSS LEADING TO SHOCKLIKE CONDITIONS WITH NONPROTEIN NITROGEN RETENTION**
- 1 Diarrhea
 - a Prolonged
 - b Excessive
 - 2 Upper intestinal obstruction (fecal vomiting is unlikely in adrenal insufficiency)
 - 3 Ileostomy
 - 4 Diabetic acidosis
- XV COMPLICATIONS SEQUELAE OR ASSOCIATED DISEASES**
- A TUBERCULOSIS** (70 to 80% with adrenal tuberculosis)⁹
- 1 Pulmonary
 - 2 Glandular
 - 3 Renal
 - 4 Osseous
 - 5 Intestinal
 - 6 Viliary
- B CARCINOMA**
- 1 Adrenals primarily involved
 - 2 Metastatic
- C ADRENAL CRISIS PRECIPITATED BY**
- 1 Acute infection
 - a Tonsillitis
 - b Bronchopneumonia
 - c Pneumonia
 - d Dental sepsis with or without ex traction (see Fig 278)
 - 2 Trauma
 - 3 Anesthesia
 - 4 Operation
- D OVERTREATMENT WITH**
- 1 Salt
 - a Edema may develop
 - b Blood pressure does not increase
 - 2 Desoxycorticosterone^{10 68 122 1 3}
 - a Edema
 - b Hypertension
 - c Cardiac enlargement
 - d Pericarditis
 - e Focal myocardial necrosis
 - f Arthralgias
 - g Nephritis
- E ASSOCIATED DISEASES**
- 1 Acromegaly
 - 2 Cushing's syndrome
 - 3 Myxedema
 - 4 Hyperthyroidism^{10 18 33 44}
 - 5 Hypoparathyroidism and moniliasis³
 - 6 Adrenogenital syndrome^{103 105}
 - 7 Diabetes mellitus (see Protocol 40 XXX)^{2 3 8 7 1 14 15 17 1 34 63 74 83 84 90 92 121}

- 8 Paget's disease
- 9 Rheumatoid arthritis^{4*}
- 10 Acute infections
- 11 Ulcerative colitis
- 12 Nephritis⁷⁸
- 13 Amyloidosis⁶

XVI TREATMENT

A ACUTE ADRENAL INSUFFICIENCY AND CRISIS

- 1 Bed rest and warmth
- 2 Adrenocortical medication
 - a Indication—immediate substitution therapy
 - b Dosage
 - (1) Adrenocortical extract (aqueous), intravenous or intramuscular—25 to 100 cc or more, if patient in comatose
 - (2) Cortisone, parenteral—200 mg (may become available for intravenous use)
 - c Result—improvement with partial maintenance of blood sugar levels
- 3 Saline solution
 - a Indications
 - (1) Restoration immediately of abnormal electrolytic balance due to salt loss
 - (2) Utilizable energy provided for saving body stores
 - b Dosage intravenous—2,000 to 3 000 cc of 0.9 to 1.5 per cent solution with 10 per cent glucose/24 hrs
 - c Results—striking improvement
- 4 Epinephrine hydrochloride
 - a Aqueous solution
 - (1) Indication—to increase or maintain blood pressure
 - (2) Dosage—subcutaneous
 - (a) On admission—0.3 to 0.5 cc (1:1 000) if blood pressure is very low
 - (b) Later—repeat every 1 to 2 hrs as needed
 - (3) Results—value questionable
 - b Oil solution
 - (1) Indication—as for aqueous extracts
 - (2) Dosage subcutaneous—0.5 cc (1:500) once a day may be used in a few days in place of aqueous extracts

- (3) Results—difficult to evaluate
- 5 Nor epinephrine (arterenol)
 - a Indication—as for epinephrine
 - b Dosage, intravenous drip—0.2 mcrograms/kg of body weight/min (2 mg /1 of saline)
 - c Results—still experimental
- 6 Whole blood
 - a Indications
 - (1) Anemia
 - (2) Weight loss of marked degree
 - b Dosage, intravenous—500 cc.
 - c Results—helpful
- 7 Human albumen¹¹⁵
 - a Indications—as above
 - b Dosage, intravenous—250 cc of 5 per cent solution
 - c Results—as above
- 8 Combined intravenous therapy¹¹⁵
 - a Following may be given with 500 cc of 5 per cent glucose in normal saline solution
 - (1) Adrenal extract 50 to 100 units
 - (2) Penicillin 500 000 units
 - (3) Human albumen 25 Gm
 - b From 250 to 500 cc of the above mixture may be given slowly
- 9 Protein hydrolysates are not¹¹⁴
 - a Well tolerated
 - b Recommended
- 10 Desoxycorticosterone acetate (DOCA)¹⁰
 - a Indications
 - (1) Salt loss conserved
 - (2) Long term therapy initiated
 - b Dosage—intramuscular
 - (1) First 24 hrs—5 to 20 mg
 - (2) Later—5 mg daily
 - c Results—eliminates intravenous therapy in a few days
- 11 Penicillin¹⁰
 - a Indications
 - (1) Fever
 - (2) Combat incipient infection
 - b Dosage intramuscular—500 000 units daily
 - c Results—favorable
- 12 When improvement is sufficient
 - a Intravenous saline may be stopped
 - b Salt in capsules may be substituted orally, if tolerated by patient
 - c Cortical extract may be omitted or reduced to 5 cc a day

d Cortisone may be given orally—25 mg/24 hrs

e Pellets of DOCA implanted (see below)

B ACUTE ADRENAL INSUFFICIENCY

1 Occurring because of stress in a person maintained on DOCA therapy¹¹

2 Aqueous adrenocortical extract and/or cortisone (as above)—dosage dependent on

a Severity

b Speed of improvement

3 Saline solution intravenous—2 000 to 3 000 cc of 5 or 10 per cent glucose with saline (not over 10 Gm of salt/24 hrs)

4 Human plasma intravenous—250 cc¹¹³

5 Human albumen intravenous—500 to 1 000 cc of 5 per cent solution¹¹³

6 Potassium phosphate solution¹¹

a Mixture

(1) K_2HPO_4 2.0 Gm

(2) KH_2PO_4 0.4 Gm

(3) Glucose solution 10 per cent

b Addenda

(1) Human plasma

(2) Human albumen

7 Desoxycorticosterone acetate (DOCA) may be administered parenterally if reason to believe pellets are exhausted or inadequate

8 Penicillin—as above

C CHRONIC ADRENAL INSUFFICIENCY

1 Sodium chloride or sodium citrate

a Indications

(1) Relatively mild cases

(2) If no danger of crisis

(3) Better protection is afforded if DOCA is given even in mild cases

b Dosage

(1) Oral (capsules or enteric coated tablets)—0.5 to 1 Gm

(2) Wilder's solution*—50 to 100 cc a day depending on amount necessary to overcome acidosis

c Results

(1) Mild cases may be maintained with salt alone^{10 96}

* Citric acid 140 Gm

Sodium citrate 98 Gm

Water 1 000 cc

(2) Salt alone will not cause hypertension

(3) If optimal effects are not attained DOCA should be used (see below)

2 Desoxycorticosterone acetate (DOCA)
30 37 66 1.0 1.1 1.3 1.6 1.7

a Indications

(1) Patients who cannot be maintained with sodium therapy alone

(2) Preferred in all cases (see Protocol 40 XXX)

b Dosage

(1) Sublingual (not recommended)
(a) Tablets 1 mg every 2 hrs a day

(b) Propylene glycol alcohol (6 drops = 1 mg) As above¹³⁰

(2) Intramuscular (2 or 5 mg in oil) 2 to 5 mg a day or every other day

(3) Pellets (75 or 125 mg each) 1 to 6 (see below)

c Method for determining dosage

(1) Parenteral route may be used to determine daily requirement although this is not necessary

(a) DOCA is injected daily in doses of 2.5 mg in oil

(b) Salt is used also about 1 Gm tid

(c) If there is no gain in weight in 3 days increase DOCA to 4 mg daily

(d) If the weight gain exceeds 0.5 kg a day or there is edema reduce the dose

(e) Injections may be used until patient is stabilized and then pellets are implanted

(f) One pellet should be used for each 0.3 mg a day

(2) Two (75 mg) pellets may be implanted safely if daily requirement is not known

(3) Average number required is 2 to 6 pellets

(4) If nonabsorption occurs or with exhaustion of pellets there is a

- (a) Weight loss
- (b) Fall in blood pressure
- d Renewal of pellets (see Protocol 40, XXX)
- (1) This should be done when patient notes a
 - (a) Change in feeling of well being
 - (b) Weight loss
 - (c) Anorexia
- (2) Two to four (75 mg) pellets are usually sufficient for this purpose, depending on previous course
- e Results
 - (1) Deliverance of 'hormone' from pellets
 - (a) Dependent on surface exposed and bodily needs
 - (b) Duration of effectiveness varies from 9 to 15 months
 - (2) Blood pressure rises
 - (3) Weight increases
 - (4) General health improves
- f Complications¹¹⁰
 - (1) Muscular weakness
 - (2) Tendon contractures
 - (3) Arthralgia
 - (4) Calcification of ear cartilages
- 3 Testosterone preparations^{8 10 e 103}
 - a Indication—in conjunction with DOCA for additional benefits
 - b Dosage (see Table 119 p 1,521)
 - (1) Sublingual or buccal tablets (methyltestosterone—10 mg each) 10 to 30 mg a day
 - (2) Tablets (methyltestosterone—10 mg each) 20 to 60 mg a day
 - (3) Parenteral (testosterone propionate—25 mg) 25 mg 3 to 6 times weekly
 - (4) Pellets (testosterone—75 mg) 4 (average)
 - c Results⁴⁵
 - (1) Strength increases
 - (2) Weight gain
 - (3) General well being improves
- 4 Adrenocortical extracts
 - a Indications (expense precludes its use in most cases)
 - (1) Acute febrile disease
 - (2) Active tuberculosis
 - (3) Preoperatively and postoperatively, including dental surgery or extraction
 - b Preparations
 - (1) Adrenal cortical extracts
 - (a) Available commercially
 - (b) Contents are an assortment of cortical steroids which affect mineral as well as carbohydrate metabolism
 - (c) One analysis revealed around 10 mg of identified steroids per 50 cc of extract¹⁰⁷
 - (2) Aqueous extracts (parenteral)¹¹³
 - (a) Source—beef adrenals
 - (b) Twelve to 16 cc are equivalent to 1 mg of DOCA for salt metabolism
 - (3) Extract prepared in oil for parenteral use only¹¹³
 - (a) Source—hog adrenals
 - (b) Three cc are equivalent to 1 mg of DOCA for salt metabolism
 - c Dosage
 - (1) Aqueous solution (subcutaneous or intravenous)—20 to 50 units or cc in divided doses per day 3 to 7 times a week
 - (2) Oil preparation (intramuscular absorbed more slowly)—4 to 6 cc per day 3 to 7 times a week
 - d Results—as other preparations, except
 - (1) More effective as regards carbohydrate metabolism on account of 11 and 17 oxysteroid compounds^{108 1-5}
 - (2) Quicker in action
- 5 Cortisone (see 107 VIII M)
 - a Indications
 - (1) Supplemental to desoxycortosterone therapy
 - (2) Pellets unnecessary
 - b Source—synthetic (from bile acids)
 - c Preparation—oral tablets
 - d Dosage—15 to 25 mg daily

6 Diet

- a Low potassium diet is theoretically desirable but not actually necessary
- b Long periods of fasting should be avoided to prevent hypoglycemia therefore frequent feedings are advisable
- c Adequate caloric intake should be urged
- d Moderate carbohydrate and high protein diet should lessen the tendency to overproduction of insulin in view of
 - (1) Insulin sensitivity
 - (2) Rapid protein and fat conversion into sugar

7 Patient should have periodic examinations particularly during first few months of treatment

- a The following should be checked
 - (1) Weight
 - (2) Edema
 - (3) Blood pressure
 - (4) Pulse
 - (5) Heart size
 - (6) Fever
 - (7) Sedimentation rate
- b A rising blood pressure and edema which can be stopped before becoming marked are signs of DOCA overdosage (see below)
- c Extreme loss of potassium may cause profound muscular weakness and flaccid paralysis due to^{116 123}
 - (1) General anesthesia
 - (2) Intravenous glucose
 - (3) Diarrhea
- d Patient should consult physician about any unusual variation in his condition or daily feeling of well being

D OVERDOSAGE OF DOCA OR SALT

- 1 Headache hypertension cardiac enlargement edema
 - a Salt intake stopped
- b DOCA
 - (1) Injections are omitted temporarily
 - (2) Pellets may have to be removed
- c Ammonium chloride oral (enteric coated tablets)—15 gr 4 to 6 times a day
- d Potassium citrate (instead of am-

monium chloride) oral—4 to 8 cc in a 20 per cent solution in fruit juice 2 to 3 times a day¹¹⁷

- e Adrenal cortical extract if needed
- f Mercurial diuretics

(1) Indication—in a grave condition, but its usage is not recommended¹¹⁷

(2) Dosage intramuscular or intravenous— $\frac{1}{2}$ to 1 cc

2 Muscular weakness tendon contractions and/or arthralgia¹¹⁸

- a DOCA—discontinue or reduce dosage
- b Adrenal cortical extract or cortisone may be substituted
- c Potassium salts as above

3 Gynecomastia may develop¹⁷ (also with adrenocortical extract⁶)

E CAUSES AND PREVENTION OF ADRENAL CRISIS

- 1 Careful adherence to program of treatment
- 2 Avoidance of unusual feats of
 - a Physical performance
 - b Severe emotional experiences
- 3 Safeguard against infection following tooth extraction and surgical operations by
 - a Penicillin or sulfa drugs prophylactically
 - b Protective dose of adrenal cortical extract or cortisone
 - c Adequate salt intake
 - d Saline and glucose infusions preoperatively and postoperatively
 - e Sufficient food intake especially the preceding night
- 4 With the onset of an acute upper respiratory infection patient should be instructed to
 - a Call physician
 - b Eat well
 - c Force fluids (fruit juices)
 - d Go to bed
 - e Keep warm
 - f Continue outlined therapy
 - g Take oral penicillin
 - (1) Should be kept on hand
 - (2) 200 000 units every 2 hrs in manner usually prescribed
- 5 Avoidance of
 - a Desiccated thyroid

- b Opiates
- Barbiturates
- d Paraldehyde
- Bromides
- f Insulin
- g Atropine
- h Histamine
- 6 Strict care in use of insulin, if also diabetic

F PREGNANCY⁸⁹

- 1 Early months of pregnancy and period of parturition present greatest hazards
- 2 Fetal adrenals may provide some replacement for mother's deficiency of adrenal hormones
- 3 Nausea and vomiting produce greater need for revised therapy
- 4 Management
 - a General—see above
 - b Delivery
 - (1) Before—treat as for impending crisis
 - (2) After—continue with same program for several days

G DIABETES^{3 6 7 1 14 15 17 18 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100}

- 1 Association of the two diseases is rare
- 2 Diabetes mellitus may follow or precede Addison's disease or both develop simultaneously (see Protocol 40, XXX)
- 3 Water test may establish the diagnosis for adrenal insufficiency
- 4 When Addison's disease is found in a patient with diabetes mellitus, there is a reduction in (see Protocol 40, XXX)
 - a Glycosuria
 - b Hyperglycemia
 - c Insulin requirement
- 5 The marked sensitivity of patients with adrenal insufficiency to insulin persists, producing hypoglycemic attacks very readily
- 6 The insulin requirement is
 - Less when patient is treated with salt or salt and DOCA
 - b Slightly increased with adrenal cortical extract or cortisone

XVII PROGNOSIS

A GENERAL

- 1 Unpredictable outcome but generally better in recent years

2 Dependent on

- a Etiology, for outcome is worse with
 - (1) Carcinoma of adrenals
 - (2) Active tuberculosis elsewhere in body (see 40 IV) if infection
 - quiescent or stationary, then prognosis is the same as with simple adrenal cortical atrophy
- b Severity of the process
 - Associated diseases
- d Adequacy and continuity of treatment
 - Degree of carbohydrate disturbance
- f Onset of symptoms
 - (1) Prognosis ■ good if the only signs are
 - (a) Pigmentation—a sudden increase may herald greater cortical loss⁹⁰
 - (b) Hypotension
 - (2) Prognosis is poorer with
 - (a) Gastro intestinal symptoms
 - (b) Weight loss
 - (c) Asthenia
 - (d) Fever
- 3 Age is not a factor, for life expectancy under 35 years is the same as in older group

B LIFE SPAN WITH THERAPY

- 1 Before modern methods—average about 12 months
- 2 With modern methods (since 1939)
 - a Average about 35 months¹⁰
 - b Fifty per cent survive 7 years¹¹⁹

XVIII CAUSES OF DEATH

A GENERAL

- 1 Acute adrenal insufficiency leads to death in itself due to a multiplicity of hormonal deficiencies
 - Shock
 - b Cerebral anoxemia
 - Renal failure
 - d Hypoglycemia⁴
 - e Cardiac arrest possibly from low serum potassium¹¹⁸
- 2 Death may occur in coma even if blood sugar and electrolytic levels remain normal¹¹⁸
- 3 Acute fulminating infections⁴
- 4 Tooth extraction
- 5 Upper respiratory infection

ADDISON'S DISEASE WITH AN APPARENT ARREST
OF 6 YEARS' DURATION

Protocol XXX

Chief complaints For a year nausea, vomiting, epigastric pain weakness and loss of weight

Physical examination Age 47, female Weight 114 lbs BP 90/10 Skin diffusely pigmented, but without involvement of mucous membranes

Laboratory data RBC 4,900,000 Hgb 100% NPN 54 mg % Adrenal water test night volume 300 cc and day urine 8 30 A.M.—0 9 30 A.M.—94 cc 10 30 A.M.—27 cc 11 30 A.M.—21 cc 12 30 P.M.—15 cc Urine chloride 247 mg % Blood chloride 528 mg % Urine urea nitrogen 153 mg % Blood urea nitrogen 41.2 mg % Factor A = 3

Treatment Admitted to hospital Intravenous saline and glucose NPN decreased to 35 mg % Daily injection of DOCA followed by pellet implantation of 750 mg of DOCA Salt tablets could not be tolerated but liberal supply was used on food

Progress

YEARS

- 5 No further treatment except salt Patient was well and active Marked loss

of pigmentation Weight rose to 132 lbs and remained there BP never below 140/80 Pellets not palpable Adrenal water test night urine over 100 cc, day urine 8 30 A.M.—50 cc 9 30 A.M.—150 cc 10 30 A.M.—150 cc, 11 30 A.M.—150 cc, 12 30 P.M.—160 cc

- 6 Patient began to lose weight and BP fell Gradual onset of asthenia Water test—Part I night urine 900 cc, day urine 9 30 A.M.—20 cc 10 30 A.M.—40 cc, 11 30 A.M.—20 cc Positive results 17 Letosteroids 0.5 to 4.8/24 hrs Pellets of DOCA (300 mg) implanted with immediate improvement which has been maintained

Comment Several explanations of the prolonged benefit of pellets are possible The pellets may actually have lasted the entire period or a functional strain on remnants of adrenal cortical tissue was relieved which with rest were able to carry on until insufficiency again developed possibly from an acute infection that was not noticed by patient

HYPERTHYROIDISM DIABETES MELLITUS AND
ADDISON'S DISEASE

Protocol XXX

History of present illness Age 33 female Hyperthyroidism (BMR plus 67 and plus 24%) and diabetes (fasting blood sugar 280 mg %) She was prepared with iodine and then had a subtotal thyroidectomy Subsequent BMR done each year for 5 years ranged from minus 4 to plus 11%

Treatment Diabetes was controlled with 10 units of protamine zinc insulin the first year 15 units the second year and the final average dose was 25 units

Progress

YEARS

- 10 Patient had the grippe and diabetic acidosis Insulin requirement was increased to 50 to 70 units a day and subsequently was dropped to 15 units

of protamine zinc insulin and 10 units of regular insulin

- 10% She noted a poor appetite, 6 lbs loss in weight pains in her legs and pigmentation of her skin Fasting blood sugar levels varied from 56 to 330 mg % Positive adrenal water test She was put on salt and advised to return for pellet implantation but before this was possible patient began to vomit and failed to report this to her physician She became semicomatose which was not due to insulin and died despite emergency treatment

Comment Pellet implantation of desoxycorticosterone is always advisable as soon as possible when severe diabetes is present with Addison's disease

ACUTE ADRENAL INSUFFICIENCY FROM PRESUMED METASTATIC CARCINOMA OF THE LUNGS

PROTOCOL XXXI

Family history Negative*Past medical* Duodenal ulcer 8 years before*Chief complaints* Rather sudden onset of anorexia, nausea and vomiting and weight loss of 30 lbs*Physical examination* Age 45, male BP 110/70 Weak Slight tanning of skin No black freckles, but some brownish pigment of mucosa of mouth and gums Small supra clavicular lymph gland*Laboratory data* RBC 4,200,000 Hgb 10.8 Gm WBC 7,200 Differential polymorpho nuclears 69%, lymphocytes 24%, cosino

phils 7% Sodium chloride 528 mg % Water test positive, A factor 5.6 Biopsy of lymph node—metastatic undifferentiated carcinoma

Röntgenographic findings Lobulated mass arising in left mediastinum and extending to apex Probable carcinoma*Treatment* Intravenous saline, lipoadrenal extract, desoxycorticosterone and penicillin Temperature rose to 105° Pneumonic area in right lung Sudden death*Comment* Fifteen per cent of carcinomas of the lung metastasize to the adrenal glands⁹

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FIG 270 ADDISON'S DISEASE (Left) Picture of original case (Henry Patten) of Thomas Addison (Right) Organs of same patient (Top) Diseased suprarenal capsules in situ (Bottom) Sections of suprarenal capsules (Addison T. On Disease of Supra Renal Capsules London Samuel Highley)

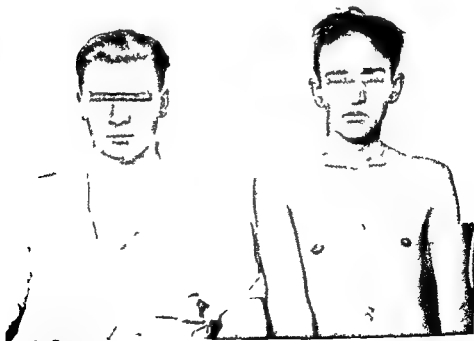


FIG 271 ADDISON'S DISEASE (See also Figs 272 and 273) A patient with Addison's disease showing generalized pigmentation compared with the normal (left)



FIG 272 ADDISON'S DISEASE (See also Figs 271 and 273) Addison's disease with marked pigmentation of arms as compared with the normal (left)



FIG 273 ADDISON'S DISEASE (See also Figs 271 and 272) Pigmentation of mucous membranes of lips. Note that beard growth is normal



FIG 274 ADDISON'S DISEASE

Chief complaints Weakness pigmentation of skin for 3 years Weight loss of 17 lbs Amenorrhea 2 years
Physical examination Age 34 female As above BP 150/90 Darkly pigmented especially about elbows knees and perineum Black freckles Loss of axillary and pubic hair

Laboratory data Positive water test
Roentgenographic findings Skull negative Chest negative No calcification of adrenals

Comment No further investigation could be done Hypopituitarism cannot be excluded as cause of adrenal insufficiency in this case but pigmentation and black freckles are in favor of primary cortical atrophy



FIG 275 RAPID PIGMENTATION OF ADRENAL INSUFFICIENCY FOLLOWING REMOVAL OF ADRENAL TUMOR

Chief complaint Gallbladder trouble for 9 years

History of present illness Repeated attacks of severe right upper quadrant pain with

nausea and vomiting Patient required hypodermics for relief No other complaints Roentgenograms showed gall stones Patient lost 30 lbs on a reduction diet

Physical examination Age 33 female BP 110/60 Normal findings

Roentgenographic findings One large gall stone and a mass 10 cm in diameter flecked with calcium

Treatment Cholecystectomy Right adrenal removed because of adrenal tumor which was reddish in color firm and speckled with areas of calcification Left adrenal was palpated and considered normal She had a severe postoperative shock but recovered with adrenal therapy

Pathologic report Cortical carcinoma with old hemorrhage and bone formation Gall stones

Progress Within a month the patient developed typical Addison's disease — bronze color numerous black freckles and pigmentation of the operative scar BP 90/60 Positive water test She was maintained on desoxycorticosterone Weight 3 years later was 130 lbs Patient working Menses normal Note marked pigmentation of hands and abdominal scar

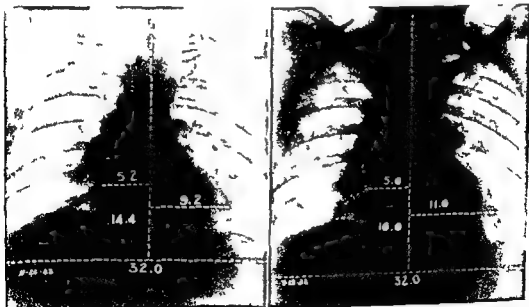


FIG 276 ADDISON'S DISEASE Heart size in 56 year old man with previous hypertension before and 7 months after treatment with desoxycorticosterone pellets (*Left*) Weight 164 lbs BP 90/60 at time of first roentgenograms Note hypertensive shape of heart (*Right*) Weight 151 lbs BP 160/110

FIG 277 ABSCESSSED TUBERCULOUS ADRENAL GLAND Adrenalectomy was performed in a patient with Addison's disease because of a tuberculous abscess. Recovery and maintenance on desoxycorticosterone.

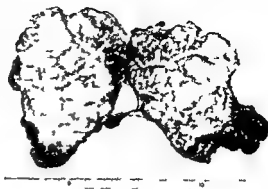


FIG 278 ADDISON'S DISEASE

History Age 40 female. Loss of weight (40 lbs) and strength. Nausea and vomiting 6 months.

Progress After hospital treatment patient did well on salt (8 gm/24 hrs) and adrenocortical extract (Wilson) 4 cc weekly. Patient felt well for 5 years until a tooth was extracted at home. After that she rapidly developed swelling and pain in the jaw and tissues of the face and neck. In spite of intravenous fluids of saline and glucose, cortical extract, sulfathiazole and DOCA patient died in 36 hrs.

Postmortem Healed tuberculosis of both adrenals. No normal adrenal tissue was found.

Comment Tooth extraction is a serious undertaking in Addison's disease. Careful preparation is of utmost importance.

(Left) Shortly after initial treatment. (Right) Several years later. Note decrease in pigmentation.

SECTION 41

WATERHOUSE-FRIDERICHSEN SYNDROME

SYNONYMS

Suprarenal apoplexy
Spontaneous suprarenal hemorrhage
Purpura fulminans

I DEFINITION

An acute hemorrhagic disease of the adrenals that occurs most frequently in infants and young children and which may be rapidly fatal

II APPEARANCE

Acutely and critically ill patient who is dyspneic, cyanotic, stuporous or comatose, showing petechiae or purpuric rash, and often signs of shock

III AGE

Infants or young children, rarely adults¹⁸

IV SEX

Either

V MENTAL DEVIATIONS

Stuporous or comatose in most cases

VI PHYSICAL STATUS

A GENERAL

- 1 Respiration
- 2 Temperature
- 3 Petechiae

Grunting

Elevated, chills frequent

First at conjunctivae, extremities, trunk, increase quickly to large purpuric rash, later confluent, when due to hemorrhagic disease of newborn, fewer spots are present¹

- 4 Color
- 5 Pulse
- 6 Blood pressure
- 7 Neurologic

Cyanosis

Rapid and shallow

Falls, circulatory collapse

May be negative later convulsions, coma, death

VII LABORATORY DATA

A URINE

- 1 Sediment
- 2 Volume

Albumin and casts may be present

Reduced

II HEMATOLOGY

- 1 Red blood cells
- 2 Hemoglobin
- 3 White blood cells
- 4 Differential

May be decreased

May be decreased

Normal to 99,500¹⁷

Increased polymorphonuclear leukocytes relative lymphopenia

- 5 Platelets
- 6 Bleeding time
- 7 Coagulation time

May be reduced

Normal¹¹

Normal¹¹

C BLOOD CHEMICAL ANALYSES

- 1 Sugar
- 2 Nonprotein nitrogen
- 3 Sodium
- 4 Potassium

May be decreased

Increased⁴

Normal, may be increased⁴

Normal may be increased⁴

Adrenals—Waterhouse Friderichsen Syndrome

- | | |
|-----------------|-------------------------------------|
| 5 Chlorides | Normal ^{6 12} |
| 6 Creatinine | Increased ⁶ |
| 7 Icterus index | Normal or increased ^{6 11} |

D MISCELLANEOUS

- 1 Blood culture
 - a Meningococcus in 50 per cent¹³
 - b Other organs have been reported but relationship is unknown
- 2 Spinal fluid

a Cells	Normal or increased rarely
b Pressure	Normal
c Culture	Meningococcus infrequently

VIII ETIOLOGY

A TYPES

- 1 Newborn
 - a Asphyxia
 - b Trauma
 - c Toxemia
 - d Syphilis
- 2 Childhood or adulthood
 - a Meningococcal septicemia without purulent meningitis - Martland is of the opinion that this organism is the sole cause of the acute syndrome¹⁸
 - b Other organisms have been reported
 - (1) Staphylococcus
 - (2) Streptococcus
 - (3) Pneumococcus
 - c Acute infections^{1 2 3 4 5 6 7 8 9 10 11 12 13}
 - (1) Diphtheria
 - (2) Scarlet fever
 - (3) Pneumonia
 - (4) Poliomyelitis
 - (5) Pemphigus
 - (6) Hemophilus influenza
 - d Heparin therapy¹⁹

IX PATHOLOGY

A GROSS AND MICROSCOPIC^{7 9 11 12 17}

- 1 Adrenals
 - a Hemorrhage
 - (1) Bilateral
 - (2) Diffuse and minute to massive with rupture of the capsule occasionally
 - b Medulla and zona reticularis are principal sites of damaged tissue
 - c Suprarenal vein thrombosis is uncommon
- 2 Skin—lesions are due to capillary and arteriolar
 - a Breakage
 - b Occlusion

3 Meninges—rarely involved even in cases due to meningococcemia

4 Brain

- a Vessels of leptomeninges are congested
- b Convulsions flattened
- c Encephalitis is not common

5 Thymus and lymph glands

- a Enlarged
- b Hyperplasia

6 Other organs—findings of a fulminating infection

X SYMPTOMATOLOGY^{1 2 3 4 5 6 7 8 9 10 11 12}

A Onset—Sudden following

- 1 Mild upper respiratory infection
- 2 Gastro-intestinal complaints (mild)
- 3 Good health

B GENERAL

- 1 Fever rises rapidly
- 2 Chill or chilly sensations
- 3 Irritability
- 4 Headache
- 5 Muscular aches
- 6 Stiffness of neck occasionally
- 7 Nausea
- 8 Vomiting
- 9 Abdominal pain
- 10 Respirations increased

C COURSE

- 1 Fulminating
- 2 Rapid downhill
- 3 Death within 24 hrs rarely 80 to 88 hrs

XI DIAGNOSIS

A HISTORY

- 1 Sudden onset of an acute illness
- 2 Few mild complaints followed by severe prostration in a short while

B FINDINGS

- 1 Vasomotor collapse
- 2 Acute adrenal insufficiency
- 3 Meningococcic infection in some cases

XII TREATMENT

A COMMENT

- 1 Immediate and vigorous therapy must be instituted because of fulminating course of the disease
- 2 Combat
 - a Acute adrenal insufficiency
 - b Infection
 - c Vasomotor collapse

B MANAGEMENT

- 1 Infection
 - a Sulfonamides
 - b Penicillin
 - c Saline and glucose (intravenous)
 - d Whole blood transfusions
- 2 Adrenal insufficiency (see 40 XVI)
 - a Whole adrenal extract¹⁵
 - b Desoxy corticosterone
 - c Cortisone—large doses

- d Saline and glucose (intravenous)
 - e Adrenalin, possibly
- 3 Miscellaneous
 - a Vitamin C, optional
 - b Oxygen, if necessary

C RESULTS OF THERAPY

- 1 Decrease in pigment ■ not due to a loss, but to improved hydration
- 2 Improvement with saline
- 3 Better effect on muscles with adrenocortical extracts than desoxycorticosterone however, the latter is very beneficial

XIII PROGNOSIS

A IN THE PAST—Fatal for all

B RECENT RESULTS—Recovered cases have been reported^{9 14 17 1}

XIV CAUSES OF DEATH

A ACUTE ADRENAL INSUFFICIENCY

B MENINGOCOCCEMIA

C UNKNOWN

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SECTION 42

THE ADRENOGENITAL SYNDROMES

I DEFINITION

A INTRODUCTION

- 1 The adrenogenital syndromes may be defined as a complex of signs and symptoms resulting from excess secretion of androgenic hormones by adrenal cortical tissue
- 2 The manifestations of the adrenogenital syndromes depend upon the
 - a Age of onset
 - b Initial sex of the individual (genetically speaking)¹⁹
 - Type and amount of hormones elaborated
- 3 The signs and symptoms are those of
 - a Precocious sexual and somatic development of young males
 - Masculinization and varying degrees of increased somatic develop-

ment in fetal, young or adult females

- 4 Except for the divergent abnormalities of the genital apparatus other changes are somewhat similar in all types
- 5 Feminization of the male due to adrenocortical hyperfunction is not usually classified under adrenogenital syndromes (although there is little doubt that it should be) (see 43 VIII XII)
- 6 Cushing's syndrome may also be due to hypercorticoadrenahum but the non androgenic cortical hormones predominate therefore it is a distinct and different clinical entity (see 11)
- 7 Achard Thiers syndrome (diabetes of bearded women) — a rare condition manifesting combined hyperadrenal corticalism of the Cushing's and adrenogenital syndromes (see 84 XIV B 5)^{1, 20}

II APPEARANCE

A JUVENILE

Variable obese muscular slightly over average height carp mouthed hirsute (see Figs 179 and 280)

B ADULT

Normal to obese, feminine or masculine configuration, fat cheeks often hirsute temporal hair recession occasionally and acne (for pseudohermaphroditism of adrenal origin see 80 IV)

III AGE

Any

IV SEX

Either but females predominate

V MENTAL DEVIATIONS

A INTELLIGENCE

Normal or below average¹⁷

B RESPONSIVENESS

Normal variations

C OTHER ABERRATIONS

Females may have male psyche

VI PHYSICAL STATUS

A NUTRITION

Normal

1 Weight

Normal

2 Fat

Masculine tendency

B STATURE

During growth period may be taller than average because of precocious development but epiphyseal closure occurs sooner so that final height is often below standard (see Fig 280 and Chart 94)^{17 24 26 29}

C EXTREMITIES

1 Upper

Normal or masculine configuration

a Hands

Proportionate to increased developmental changes

b Fingers

As above

c	Span	Normal
2	Lower	Pubis to floor may be less than pubis to head ⁴⁰
a	Feet	As above
b	Toes	As above
D	SPINE	Normal
E	INTEGUMENT	
1	General	Normal
a	Texture	Lacks baby softness
b	Temperature	Normal
c	Eruptions	Acne with virilism
d	Pigmentation	Nothing unusual
e	Color	Normal
2	Hair (see Fig 279)	
a	Head	Plentiful, low browed, later temporal recession, rarely baldness in females
b	Facial	May be increased in normal places as well as on neck, eyebrows may be heavy
c	Axillary	Normal or more than for age
d	Pubic	Increased for age, male distribution may occur in females
e	Body	Normal or increased (marked in some)
F	HEAD	
1	Shape and size	Normal
2	Facial expression	Not unusual
3	Eyes	
a	General	Normal
b	Fundi	Normal
c	Visual	
(1)	Fields	Normal
(2)	Acuity	Normal variations
4	Ears and nose	Normal
5	Mouth and throat	Normal
a	General	Normal
b	Teeth	Normal or development accelerated ¹⁷
c	Larynx (voice)	Normal or lowered
G	NECK	
1	General	Normal or thick occasionally
2	Thyroid	Normal
H	CHEST	Normal
I	HEART AND PERIPHERAL VESSELS	
1	Heart	Normal
2	Rate and rhythm	Normal
3	Blood pressure	Normal or slightly increased, rarely excessive ^{38 43}
4	Peripheral arteries and veins	Normal
5	Vasomotor	Normal
J	BREASTS	
1	Male	Normal or slightly increased due to excess fat (see below)
2	Female	Often retarded in growth or prematurely developed tendency to atrophy in adults (see below)
K	ABDOMEN	
1	Liver	Normal unless metastatic lesions
2	Spleen	Normal

3	Hernia	None
4	Tumor	Present in some cases at kidney area
L GENITALIA		
1	Male ^{7 17 20 38 41 60}	
a	Penis	Increased size in young males
b	Testes	Normal for chronologic age may increase at usual time of puberty
c	Prostate	May be enlarged for age
2	Female ^{7 9 11 33 46 48}	
a	External	Clitoris may hypertrophy to size of male penis of same age vulva enlarged (see Fig 281)
b	Internal	Retarded development in a few cases, vestigial female prostate may enlarge
M NEUROMUSCULAR		
1	Muscles	Bulk relatively increased but not always
2	Gait	Normal or strutting
3	Body movements	As if an older person
4	Tremor	None
5	Paresthesias	None
6	Reflexes	None
N SPEECH		Normal
VII LABORATORY DATA		
A URINE		
1	General	Normal
2	Special analyses	
a	Sugar	Normal
b	Albumin	Normal
c	Creatine	Increased excretion probably commensurate with muscle mass
d	Creatinine	Normal
e	Chlorides	Normal ⁴
B HEMATOLOGY		
1	Red blood cells	Normal or increased ⁴
2	Hemoglobin	Normal
3	White blood cells	May be increased
4	Differential	Normal or polymorphonuclears increased
C BLOOD CHEMICAL ANALYSES		
1	Sugar	Normal or increased ^{20 33 40 46 60}
2	Nonprotein nitrogen	Normal or increased ^{1 40 46 60}
3	Protein	Normal or decreased ⁴⁰
4	Uric acid	Normal
5	Cholesterol	Normal ^{40 60}
6	Sodium	Normal
7	Potassium	Normal
8	Calcium	Normal ^{1 3 40 46 60}
9	Phosphorus	Normal or increased for age decreased rarely ^{20 3 46 60}
10	Phosphatase	Normal ⁰
11	Chlorides	Normal ^{1 40 46}
D FUNCTION TESTS		
1	Tolerance	
a	Glucose	Normal or rarely impaired ^{7 24 40 60}

b Glucose insulin	No data
c Insulin	Normal ⁶³
2 Adrenal water	Positive, if adrenal insufficiency supervenes ^{6 60}
3 Salt deprivation	No data
4 Balance	
a Nitrogen	Most likely positive to the extent found during growth
L MISCELLANEOUS TESTS	
1 Basal metabolic rate	Normal variation, occasionally elevated ^{7 30 31 40}
2 Circulation time	No data
3 Sedimentation rate	Normal
4 Specific dynamic action of protein	No data
5 Gastric analysis	No data
6 Electrocardiogram	Normal
F URINARY HORMONE ASSAYS	
1 FSH	Not increased ^{11 49}
2 LH	No data
3 Estrogens	Variable ^{6 10 16 3 8 37 40 46 49}
4 Pregnanediol	May be positive other derivatives have been found ^{13 54}
5 17 ketosteroids	Normal ^{4 7 9 11 21 26 33 30 34 37 40} or increased ^{46 1 53 55}
a Beta fraction	Increased more in tumors than with hyperplasia ^{6 54}
b Transdehydroandrosterone	Present with tumors only ⁹
6 11 oxysteroids	Normal or slightly elevated ^{11 53 6}
7 Aschheim Zondek	May be positive with tumor ³⁹
8 TSH	No data
G BIOPSY	
1 Endometrial	Atrophic probably
2 Testicular	No data
H VAGINAL SMEAR	Poor estrin effect
I SEMEN ANALYSIS	Little data, but spermatozooids reported present in a young male ^{7 1}

VIII ROENTGENOGRAPHIC FINDINGS

A SKULL	
1 Cranial vault	Sutures may close prematurely
2 Sella turcica	Normal ¹¹
3 Sinuses	Normal
4 Mandible	Normal
5 Teeth	Normal
II EPIPHYSEAL STATUS (boneage)	Increased ossification centers are advanced ^{7 20, 34 48 60}
C LONG BONES	Normal or denser than average
D VERTEBRAE	Normal
E BONE TEXTURE	Normal or decalcification is very slight
F MISCELLANEOUS	Normal

IX ETIOLOGY

A FETAL TYPE	
1 Cause of adrenal cortical hyperplasia is unknown	
	2 It might be due to
	a Transported or elaborated androgenic hormones by the placenta
	b Abnormal stimulation from chorionic hormones (see 80 III)

B OTHER TYPES—Excess androgenic steroid production by

- 1 Adrenal cortical tumors
- 2 Pheochromocytoma with cortical hyperplasia (rare)
- 3 Idiopathic
 - a Adrenal cortical hyperplasia
 - b Hypersecretion of adrenocorticotrophic hormone possibly
- 4 Accessory adrenal cortical tissue

X PATHOLOGY

A Gross (see 39 IX A)

- 1 Adrenal cortex^{20 21 22}
 - a Enlargement in both glands without any other change
 - b Adenoma (found at autopsies without any clinical evidence)
 - (1) Bilateral often
 - (2) Spherical
 - (3) Few millimeters to several centimeters
 - (4) Deep brown
 - (5) Capsule intact
 - c Adenocarcinoma
 - (1) Larger than adenomas
 - (2) Yellow
 - (3) Capsule often broken
 - (4) Soft
 - (5) Hemorrhage
 - (6) Necrosis
 - d Aberrant cortical rests may give rise to tumors indistinguishable from those found in adrenal cortex²³
- 2 Pituitary—normal¹⁸
- 3 Thyroid—normal^{18 20}
- 4 Testes—variable²⁰
- 5 Ovaries—normal¹⁸
- 6 Metastases to
 - a Brain
 - b Lungs
 - c Liver
 - d Opposite adrenal

E Microscopic

- 1 Adrenal^{20 21 22}
 - a Hyperplasia
 - (1) Adrenal cortices uniformly enlarged
 - (2) Hyperplasia may be
 - (a) Nodular
 - (b) Circumscribed
 - (3) Normal cellular structure

b Adenoma

- (1) Normal cells
- (2) Layers are not changed

c Adenocarcinoma

- (1) Cells
 - (a) Size—variable
 - (b) Shape—all kinds
 - (c) Nuclei—dark staining
 - (d) Undifferentiated
 - (e) Mitosis
- (2) Layers can be recognized in some areas

d Adrenocortical rests—distinguishable from a group of Leydig cells by the connective tissue capsule

2 Other glands—normal

XI PATHOLOGIC PHYSIOLOGY

1 GENERAL

- 1 The bodily changes which occur in the adrenogenital syndromes are apparently due to hyperfunction of adrenocortical tissue (see 39 VI A 3)
- 2 The adrenogenital syndromes are caused chiefly by an excess production of androgenic hormones and as a rule are singularly free of abnormal effects from other adrenocortical hormones
 - a This is difficult to understand in cases where adrenal insufficiency and adrenocortical hyperplasia exist (see 39 X C 2 a (3))^{24 25 26 27 28}
 - b The more recent opinion that one pituitary adrenocorticotrophic hormone is capable of stimulating three major (and theoretical) hormones of the adrenal cortex also complicates the problem; an aberrant response is postulated²
- 3 The androgenic effects in the adrenogenital syndrome are chiefly as follows
 - a Muscle mass increases disproportionately although some cases show only accelerated
 - (1) Genital development
 - (2) Linear growth (see Fig 280 and Chart 94)
 - b Bone maturation is advanced
 - c Enlargement of clitoris or premature development of male genitalia and accessory organs
 - d Sexual and body hair are
 - (1) Increased
 - (2) Premature in appearance

- 4 Although masculinization occurs, excess of estrogens may be found in the urine
 - a This suggests that androgens are more successful in competing for the target organs than estrogens
 - b Experimental evidence, however, points to the probability that the response is a matter of concentration rather than a more selective advantage by either type of hormone
 - (1) During the growth period the penis responds readily to androgens, whereas after sexual maturity it changes very little or not at all
 - (2) The clitoris can increase in size at any time under the influence of androgens
 - (3) After sexual maturity, the female breasts do not increase from an excess of estrogen (pregnancy excepted)
 - (4) The growth of breasts is frequent in males especially after the opposing and potent androgens are eliminated by castration
 - (5) The target organs may respond equally to androgens or estrogens but experimental data favors the hypothesis that the pituitary is more sensitive to estrogens than androgens (see also inhibin 45 VI B 2)
 - c Urinary estrogen or androgen assays are not a measure of hormonal activity within the body so that deductions from these may be misleading as to the physiologic activity of circulating hormones in the blood stream³⁰
- 5 The effects of excess androgenic secretion depend on the ability of target tissues to react — a phenomenon which is conditioned by
 - a The age of the organism (from embryo to old age)
 - b Other influences
 - (1) Disease
 - (2) Genetic defects (see above and Pseudohermaphroditism 80 IV True hermaphroditism 81 IV)

XII SYMPTOMATOLOGY

A ADRENOGENITAL SYNDROME

- 1 None usually
- 2 Physical and behavior changes are noted by parents
- 3 Pain with extension of malignant tumor
- 4 Marked strength
- 5 Voice deepens
- 6 Nocturnal emission in males
- 7 Vaginal bleeding in young females
- 8 Adrenal insufficiency develops in some at a later date

B VIRILISM OF ADRENAL ORIGIN

- 1 Change in psyche
- 2 Femininity lost
- 3 Weight decreased, if due to malignant tumor
- 4 Acne
- 5 Hirsutism
- 6 Recession of hair on temples (slight to marked)
- 7 Voice lower pitched
- 8 Amenorrhea

XIII DIAGNOSIS

A MALES

- 1 Young
 - a Precocious sexual development
 - b Testes usually small for body growth
 - c 17 ketosteroids — increased out of proportion to somatic development
 - d Bone age—advanced
 - e Adrenal tumor or hyperplasia may be demonstrated
- 2 Adults
 - a Feminization
 - b Testicular hypoplasia
 - c 17 ketosteroids and urinary estrogens are excessive
 - d Adrenal
 - (1) Tumor
 - (2) Hyperplasia

B FEMALES (young or adult)

- 1 Amenorrhea
- 2 Hirsutism—usually
- 3 Clitoris—large
- 4 17 ketosteroids—excessive
- 5 Bone age—advanced
- 6 Adrenal
 - a Tumor
 - b Hyperplasia

C PSEUDHERMAPHRODISM

- 1 Male—see 80 IV A and Table 74
- 2 Female—see 80 IV B and Table 73

XIV DIFFERENTIAL DIAGNOSIS

A CHILDREN

- 1 Granulosa cell tumor (females) (see 70 VII)
 - a Mental age—normal
 - b Contours—adult female
 - c Sexual hair—may be present
 - d Body hair—normal
 - e Breast development
 - f Clitoris—enlarged
 - g Vaginal bleeding
 - h Bone age—advanced in these cases also
 - i Demonstration of tumor by
 - (1) Palpation
 - (2) Laparotomy
- 2 Idiopathic or true sexual precocity
 - a Normal in all respects, except for premature development of puberty
 - b Masculinizing tendency is absent in female
 - c Body hair is not increased
 - d Clitoris is normal for sexual age
 - e Regular menstrual cycles with normal
 - (1) Ovulation
 - (2) Luteal phase
 - (3) Fertility

f Spermatogenesis and fertility in males

g No demonstrable

(1) Adrenal

(a) Hyperplasia

(b) Tumor

(2) Tumors

(a) Ovarian

(b) Testicular

(c) Pineal

3 Sexual precocity due to other causes

a Pinealoma (see 87 VIII)

(1) Headache

(2) Intracranial pressure signs

(3) Visual loss

(4) Ocular palsy or palsies

(5) Neurologic changes due to expansion and extension of tumor

(6) Confined to boys (rare exceptions)

b Cranial injury from disease, trauma or tumor

(1) History is important

(2) Any of these may duplicate true idiopathic sexual precocity

c Testicular tumor—see 54 X

4 Cushing's syndrome—see below

5 Pseudohermaphrodisism—see below and 80 IV A B

B ADULT (females)

1 Arrhenoblastoma (see 73 VI)

a Pelvic examination or exploration reveals tumor

TABLE 54 FEMALE PSEUDHERMAPHRODISM OF ADRENOGENITAL TYPE⁴⁸

	OCCURRENCE		
	EARLY FETAL LIFE	LATE FETAL LIFE	AFTER BIRTH
Müllerian duct system	Retarded	Develops	Developed
Ovaries	Rudimentary	Rudimentary	Rudimentary
Vagina	Not visible	Visible may open into urethral hypospadias or calliculus seminales	Present
Breasts	Not developed	Not developed	Develop
Clitoris	Enlarged	Slightly enlarged	Enlarged
Hypopadias	Present	May be present (see above)	Absent
Prostate	Rudimentary	Absent	Absent
Masculinization	Present	Present	Present
Menses	Absent	Absent	Absent
Adrenal glands	Not enlarged	Not enlarged	Often very large may be 30 Gm or more glomerulosa and fasciculata zones increased may be in pelvis

- b Urinary androgens and 17 ketosteroids are excessive in either disease, but may be normal
- 2 Cushing's syndrome
 - a Masculinization is not as marked
 - b Buffalo type of obesity
 - c Striae are found in most cases
 - d Plethora
 - e Musculature not as well developed
 - f Clitoris is normal
 - g Diabetes may be discovered
 - h Bone age is most often delayed in prepubescent individual
 - 1 Osteoporosis is common
- 3 Hypertrichosis (female) (see Fig 282)
 - a Family history of hirsutism
 - b Menses—normal
 - c Virilism—absent
 - d 17 ketosteroids—may also be increased⁴⁴
- 4 Pseudohermaphroditism (see 80 IV A, B)^{48 49}
 - a Some cases of female variety are apparently of adrenal origin
 - b Anatomic abnormalities may depend on period of onset of adrenal cortical hyperfunction (see Table 54)

XV COMPLICATIONS SEQUELAE AND ASSOCIATED DISEASES

A COMPLICATIONS

- 1 None unless a malignant tumor is present
- 2 Social handicaps are obvious
- 3 Psychic trauma
- 4 Cardiovascular changes are extremely rare

B SEQUELAE

- 1 Metastases
- 2 Adrenal hemorrhage

C ASSOCIATED DISEASES

- 1 Cushing's syndrome
- 2 Pheochromocytoma
- 3 Adrenal insufficiency^{7 10 35 40}

XVI TREATMENT

A SURGICAL

- 1 Introduction
 - a Every effort should be made to establish presence or absence of a malignant tumor
 - b Duration of disorder may exclude possible malignancy in many cases

- c If no tumor is demonstrated
 - (1) Exploration is probably advisable
 - (2) Bilateral resection of the adrenals should not be attempted until both adrenals have been identified^{4 12 41 43}
 - (3) Some advocate removal of one whole adrenal, leaving other intact
 - (4) Since bilateral resection may be hazardous, this should not be undertaken unless condition warrants it and only by an experienced surgeon
- d Mild hyperplasia or small adenoma of adrenal do not require any operative procedure

2 Preparation of patient

- a Special precaution should be taken to prevent adrenal insufficiency after operation although unlikely, it is possible (see 40 XVI E)
- b Preoperative treatment with testosterone propionate (intramuscular)
 - (1) Indication—for anabolic effect to counteract catabolic phenomena during postoperative course (debatable)
 - (2) Dosage
 - (a) Intramuscular
 - [1] Adults—25 mg/24 hrs
 - [2] Children—1 mg/10 lbs body weight/24 hrs
 - (b) Duration—10 days before operation

3 Results^{23 48}

- a Tumor—excellent if removable rarely no change⁴⁵
 - (1) Regression of androgenic effects
 - (2) Normal development subsequently except as limited by advanced bone age
 - (3) Relief of diabetes if present⁵
- b Hyperplasia—variable but often not too successful

B ROENTGEN

- 1 Adrenal carcinoma—generally resistant to irradiation but advisable postoperatively
- 2 Inoperable cases—possibly some value
- 3 Hyperplasia—not beneficial

C HORMONAL

1 Estrogens^{13, 41, 42}

- a Indication—girls with adrenal hy perplasia
- b Dosage (stilbestrol or other similar preparations), oral—0.2 to 0.5 mg daily (or more)

c. Results

- (1) Decrease in
 - (a) Acne
 - (b) Size of clitoris
- (2) Increase in
 - (a) Breasts
 - (b) Labia
 - (c) Female psyche

2 Progesterone

- a Indication—adjunct to estrogen therapy
- b Dosage oral (buccal)—30 mg daily for 5 days following 21 to 25 days of estrogens

c Results—as above

3 Cortisone⁴³⁻⁴⁵

- a Indication—males or females with adrenal hyperplasia
- b Dosage
 - (1) Infants—25 to 50 mg
 - (2) Older children
 - (a) Initially—50 to 100 mg
 - (b) Maintenance—10 to 25 mg

c. Results

- (1) Masculinization recedes
- (2) 17 ketosteroids decrease
- (3) Bone age retarded
- (4) Most favorable responses to date compared with other forms of treatment

XVII PROGNOSIS

A SUMMARY

- 1 Eventual outcome depends on pathol ogy of adrenal
 - a Hyperplasia—may live normal life span
 - b Carcinoma—the following factors must be considered
 - (1) Duration of disease
 - (2) Presence of metastases
 - (3) Results of therapy (see above)
 - (a) Removal of all tumor cells
 - (b) Survival from possible post operative shock
 - c Adenoma—either course as above may be taken
- 2 Therapeutic result is an influencing factor

XVIII CAUSES OF DEATH

A ADRENAL INSUFFICIENCY

B POSTOPERATIVE SHOCK

C METASTASES⁴⁶

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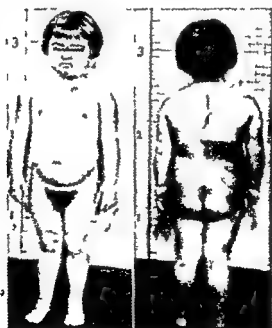


FIG 279 ADRENOGENITAL SYNDROME FROM ADRENOCORTICAL TUMOR Age 4½ female Note masculine configuration and swirls of hair (Meakins J C Practice of Medicine St Louis Mosby p 901 Photograph furnished by Dr Hector Mortimer)



FIG 280 ADRENOGENITAL SYNDROME
(See also Chart 94)

Chief complaint Precocity

Left

History of present illness Weight at birth 7 lbs 12 oz Onset at 1 year Walked at 14 months Recurrent tonsillitis and pneumonia Six year molars erupted at 3 years Perfectly well

Physical examination Age 3 Weight 45 lbs Height 43 in Height age 5 years

Laboratory data Blood count normal Eosinophils 6.5% Hinton negative Urinary 17 ketosteroids 14.6 mg/24 hrs

Röntgenographic findings Skull negative Sella 8 x 9 mm which is large for his age

Treatment None

Progress 2 years Weight 67 lbs Height 54 in Height age 11 years Adult size genitalia Body and axillary hair present

Right

5 years Weight 98 lbs Height 64 in Span 65½ in Pubic and axillary hair Body hair and fine facial lanugo Testes volume 5.5 to 8.5 cc Urinary 17 ketosteroids—total 54 mg/24 hrs alpha steroids 53 mg and beta steroids 100 mg Serum

phosphorus 4 mg % Total eosinophil count 38/cumm Bone age 15 years 3 months Ilac crests open Patient in good health except for asthma in summer Morning erections occasional emissions

Comment Patient is intelligent in fourth grade and does very well He is not virile so to speak but rather timid and shy It is unlikely that this is a simple precocious development The excess of 17 ketosteroids is unusual and suggests an adrenocortical hyperplasia The low amount of beta steroids is against this Testicular biopsy would be helpful in that Leydig cells should be present if 17 ketosteroids are of testicular origin Final height should not be more than 66 or 67 in

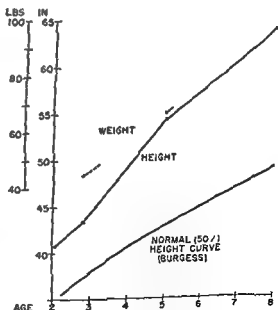


CHART 94 GROWTH CURVE OF BOY WITH ADRENOGENITAL SYNDROME (See also Fig 280) Height age of 15 years at chronologic age of 8 years



FIG 281 ADRENOGENITAL SYNDROME—CONGENITAL ADRENAL CORTICAL HYPERPLASIA

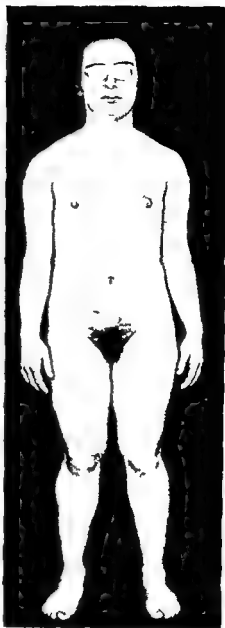
Chief Complaint Hirsutism

Family History Negative

Past History Patient born with enlarged clitoris. During past 2 years there has been excessive body and facial hair growth as well as appearance of pubic hair. Only 1 in of growth this past year. Excellent student.

Physical examination Age 13 years. Height 56 3/4 in. Weight 111 lbs. BP 138/78. Body configuration and other features as shown in photograph. Height age 11 years. Opening below clitoris probably urogenital sinus. Boogie entered bladder. Bimanual examination disclosed no uterus although this may be present.

Laboratory data Urine negative. Hgb 110% or 15.4 Gm. % RBC 5.515.000. WBC 7.900. Differential count normal. Total eosinophil count 13/cumm. Blood sugar 5 hrs p.c. 100 mg. % Serum phosphorus 2.8 mg. % 17 ketosteroids



51.2, 48.6 and 75.9 mg/24 hrs on 3 occasions. Beta steroid fraction 0. Urinary pregnandiol positive. Urinary 11 oxysteroids 0.189/100 cc. *Roentgenographic findings* Skull normal. Radial epiphyses closed. *Treatment advised* Cortisone 25 to 50 mg daily as advocated by Wilkins et al.¹¹



FIG 282 HYPERTRICHOSIS FOLLOWING SUBTOTAL THYROIDECTOMY FOR PRIMARY HYPERTHYROIDISM (See also Fig 172)

Family history Negative

Past medical Scarlet fever and tonsillitis

Chief complaints Nervousness palpitations and weight loss

History of present illness Patient has not been well for a period of 6 months. She has noticed a great deal of shortness of breath and palpitation on exertion.

Physical examination Age 17 Single Weight 96 lbs Pulse 140 BP 140/86 Skin warm and moist Thyroid small firm and symmetrically enlarged

Laboratory data BMR plus 31% and plus 21%

Diagnosis Primary hyperthyroidism

Treatment A subtotal thyroidectomy was done in 2 stages

Pathologic report Primary hyperplasia with irregular involution

Progress

MONTHS

12 Pulse 64 BMR minus 25% Feels fine

18 Complaints pain in right side of the abdomen and leg, chilliness, lethargy increased growth of hair on her face irregularity of periods and acne. Adrenal tumor or basophilism was considered. Improved on 1 gr of desiccated thyroid (U.S.P.) daily.

24 Patient in well. Periods normal. Hair continued to grow.

26 Bilateral adrenal exploration revealed nothing unusual. Biopsy specimens from the adrenals were normal. There was no change in hair growth.

44 Patient stopped thyroid medication and myxedema returned. Plasma cholesterol 358 mg %.

46 Patient seemed better while taking desiccated thyroid. Plasma cholesterol 169 mg %.

82 Antuwin S given by her family physician with no improvement. Mentally depressed. No desiccated thyroid taken. Hair about the same. Roentgenogram of skull showed arteriosclerosis involving the left internal carotid.

Follow up note Examined at Boston Dispensary for same complaints. Growth of long hair particularly on the sides of her face and chin. Male escutcheon. Abundant hair on the extremities. Clitoris normal.

Laboratory data Normal urine, complete blood count, serum protein, cholesterol, sodium and chloride. Glucose tolerance test normal. BMR—minus 44% and minus 38%. EKG—sinus arrhythmia. Urinary androgens 200 which was considered normal.

Roentgenographic findings Skull, dorsal spine, chest and adrenals revealed nothing abnormal.

Diagnosis Unexplained hirsutism, psychosis and hypothyroidism.

Follow up note Patient died a year or so later in a mental institution. No further data obtained.

Comment As in so many cases of excessive hair growth, no cause was determined. Postoperative myxedema may have stimulated hair growth, but there was no regression on administering desiccated thyroid.

SECTION 43

FEMINIZING SYNDROME DUE TO MALIGNANT ADRENAL CORTICAL TUMOR

I DEFINITION

A syndrome characterized by development of the breasts in males, occasionally with lactation, and loss of sexual function, due to a malignant adrenal cortical tumor although suspected in some instances of being the result of an excess adrenal cortical function without tumor, this has not been proven¹

II APPEARANCE

May gain weight and lose masculine facies

III AGE

Reported from 15 to 53 years, one case in a 5 year old boy¹

IV MENTAL DEVIATIONS

None or feminine psyche

V PHYSICAL STATUS

A INTEGUMENT

1 General

a Eruptions

Acne may develop

b Pigmentation

Face and abdominal linea fusca rarely^{1 4 6 28}

2 HAIR^{2 9 16 18}

a Beard

Less than usual

b Pubic

Decreased

c Body

May be lost

B BREASTS

Enlarged areolae well developed, superficial veins may be prominent milk or watery discharge may be expressed, tenderness sometimes^{1 2 7 8 10 14 18}

C ABDOMEN

1 Tumor

May be palpated

2 Liver

Normal or may be enlarged from metastatic lesions

D GENITALIA

1 Penis

Reduced in size

2 Testes

Soft and small^{6 9 10 14 18}

VI LABORATORY DATA

A GENERAL (urine hematology, blood chemical analyses)

Normal

B URINARY HORMONE ASSAYS

1 FSH

Negative or increased^{10 1}

2 Estrogens

Small or large amounts^{8 9 10 1}

3 17 ketosteroids

Slight increase, beta steroids may be increased^{10 11}

4 Aschheim Zondek

Negative in one case¹²

5 Friedman

Positive or negative^{2 8}

VII ROENTGENOGRAPHIC FINDINGS

A EPIPHYSEAL STATUS (bone age)

In Wilkins case 5 year old boy the bone age was advanced to 10 years, although the 17 ketosteroid excretion was not increased¹⁵

VIII ETIOLOGY

A UNKNOWN

B ADRENAL TUMOR (see 39 I \ A, 42 \)

C MIXED TUMOR—renal origin (see Protocol 43, \ \ \ II)

IX PATHOLOGY

A GROSS AND MICROSCOPIC

1 Tumor

a Types

- (1) Malignant adrenal cortical tumor is most common
- (2) Mixed tumor of urogenital ridge⁶
- (3) Adrenal rest tumor of testis^{9 12}

b Characteristics¹⁵

- (1) Sharply outlined
- (2) Extension to
 - (a) Surrounding structures
 - (b) Liver
- (3) Calcification may be present
- (4) Cells
 - (a) Size—variable
 - (b) Shape—all kinds
 - (c) Nuclei—hyperchromatic
 - (d) Mitotic figures in malignant cases

2 Testes

- a Good spermatogenesis with few Leydig cells¹
- b Atrophic tubular tissue with few or absent Leydig cells^{6 10 11}

3 Breasts—typical histologic changes as those of a female lactating breast^{14 16} much periductal fibrous stroma in some¹⁵

X PATHOLOGIC PHYSIOLOGY

A SUMMARY

- 1 Changes are apparently due to
 - a Increased estrogens competing for end organ response
 - b Inhibition of pituitary gonadotropic hormones
- 2 Excess of urinary estrogens are not demonstrable in all cases

XI SYMPTOMATOLOGY

A GENERAL

- 1 Breasts
 - a Enlargement
 - b Tenderness
- 2 Hair—decreased

3 Sexual function—lost^{2 5 9 14}

4 Pain from tumor

XII DIAGNOSIS

A GENERAL

- 1 Gynecomastia
- 2 Genitalia—smaller than normal
- 3 Sexual hair—decreased
- 4 Abdominal mass may be
 - a Palpable
 - b Found in roentgenogram
- 5 Exploratory laparotomy may be required

XIII DIFFERENTIAL DIAGNOSIS

A GYNECOMASTIA

- 1 With aspermia (see 51)
 - a Condition present since puberty
 - b Potentia normal
- 2 Associated with
 - a Testicular tumors (see 54 IV B)
 - b Liver disease
 - c Other pathology—see 102 \ I
 - d Idiopathic type (spermatogenesis present)
 - e Starvation

XIV COMPLICATIONS

A GENERAL

- 1 Metastases to^{2 15}
 - a Adjacent structures
 - b Kidneys
 - c Liver
 - d Spleen
 - e Lungs

B PAIN DUE TO MALIGNANT TUMOR

XV TREATMENT

A GENERAL

- 1 Surgical—removal of tumor if possible
- 2 Roentgen
 - a Tumor may be radiosensitive temporarily
 - b Postoperatively even if tumor is removed

B RESULTS

- 1 Enlargement of breasts
 - a Decreases⁹
 - b Disappears
- 2 Return of sex function even in those who ultimately succumb to metastases
- 3 Estrogens decrease in urine^{2 12}

XVI PROGNOSIS

A GENERAL

- 1 Good outlook
 - If tumor can be completely extirpated
- b Two cases recovered after successful removal of^a 15

(1) Adrenal tumor

(2) Adrenal rest tumor of testis

- 2 High incidence of malignancy in majority

XVII CAUSES OF DEATH

A METASTASES

GYNECOMASTIA AND TESTICULAR ATROPHY— Protocol XXXII Fig 283
A CASE ASSOCIATED WITH MIXED TUMOR OF RENAL ORIGIN

Family history Negative

Past medical Negative

History of present illness: Enlargement of the breasts noted for 2 years. Complained of pain in the back and right shoulder and loss of libido

Physical examination: Age 38 male married. Facial axillary and pubic hair normal. Breasts enlarged with pigmented areolae. Testes smaller than normal and soft. Prostate gland normal. Large mass was felt in the right upper quadrant.

Laboratory data: Complete blood count and urine normal. Urine FSH unsatisfactory twice. blood FSH negative on admission. Urine estrogens: admission 2 plus, 2 weeks later the same, 3 weeks later 60 r u*. Blood estrogens 1 plus on admission.

Roentgenographic findings: Chest normal. Urograms—tumor mass pressing the right kidney down and anteriorly.

Treatment: Exploration revealed inoperable tumor involving liver. Roentgen therapy produced only temporary recession in the palpable mass.

Postmortem findings: Testes—marked atrophy. The tubules showed dense hyalinized basement membranes which were partially lined by a layer of polyhedral cells with shrunken hyperchromatic nuclei with a clear cytoplasm that was granulated and vacuolated. Interstitial cells were decreased in number. No evidence of spermatogenesis. Prostate normal. Liver—3000 Gm. Right lobe was largely replaced by a tumor which bulged through the capsule. Areas of necrosis and hemorrhage as well as cystic degeneration were found. There was yellow gelatinous fluid in the tumor. The tumor mass itself weighed 1900 Gm and extended anterior to and above the right

kidney and into the diaphragmatic hiatus. Lungs and skull had metastatic nodules. Pituitary and adrenal glands are normal grossly and microscopically. Breast tissue was firm and measured about 9 cm in diameter. Microscopic sections showed many branching ducts with small amounts of pink granular material in some. Loose connective tissue stroma contained a few fibroblasts. There were also some areas of dense collagenous tissue. Arrangement was orderly and well defined basement membranes were present. A rare mitotic figure was seen. Several microscopic sections of the tumor were markedly necrotic with islands of viable tissue particularly about the vessels. The cells were arranged in sheets in some places while in others there was an attempt at gland formation and long cords. The tumor was quite vascular with very little stroma but where any intercellular tissue had been laid down it was loose. The cell nuclei were rich in chromatin and had small round or oval nucleoli. Cell membranes were not distinct, the cytoplasm was scant light in color and contained vacuoles. There were a few small groups of tumor cells growing along perineural lymphatics.

Comment: The presence of urinary estrogens in this case may have been due to inactivation of normal estrogens because of liver damage or may have originated in the tumor although none was found in extracts of the latter. The gynecomastia may not have been related to estrogens but to factors similar to those causing it in Klinefelter's syndrome. Although there was some decrease in Leydig cells beard growth continued to be heavy.

Summary: A case of gynecomastia associated with mixed tumor of renal origin with extensive metastases to the liver and testicular tubular atrophy.

* Assayed by Drs G V S and O W Smith, Fearing Research Lab, Brookline, Mass.

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FIG 283 GYNECOMASTIA TESTICULAR ATROPHY AND WILMS'S TUMOR OF RENAL (PRONEPHROS) ORIGIN (See also Protocol 43 XXXII) Age 38 Patient complained of enlarging breasts loss of libido and back ache Beard and body hair normal Abdominal mass Soft atrophic testes Urinary FSH negative Blood and urine estron gave a positive reaction Androgens not determined Postmortem examination Tumor had long cords and acini of polyhedral cells Breasts—numerous clusters of branching ducts without acini Testes—marked atrophy of tubules but with Sertoli cells and decrease in Leydig cells (Hurxthal L M and Musuhn N Gynecomastia A case associated with mixed tumor of renal origin and testicular atrophy Lahey Clin Bull 4 38 44)

SECTION 44

HYPERFUNCTION OF ADRENAL MEDULLARY OR OTHER CHROMAFFIN TISSUE DUE TO PHEOCHROMOCYTOMA

SYNONYMS

Paroxysmal or sustained hypertension Hypertepanephrrism
Hyperchromaffinism

I DEFINITION

A condition caused by excess secretion of epinephrine due to a chromaffin tumor of the adrenal medulla or accessory adrenal tissue and characterized by attacks of increased blood pressure which eventually becomes sustained (11%) few cases reported as asymptomatic and without hypertension¹¹

II APPEARANCE

As a rule nothing characteristic healthy appearance rarely adrenocortical features are present⁴⁰

III AGE

Most frequently occurs between 20 and 50 ¹¹ youngest around 2 years⁴ and oldest 82 years⁶⁸

IV SEX

Slight predominance of females

V MENTAL DEVIATIONS

A INTELLIGENCE

Normal variations

B RESPONSIVENESS

Normal

C OTHER ABERRATIONS

May seem neurotic or confused disoriented during attacks or late in disorder

VI PHYSICAL STATUS

A NUTRITION

Normal

1 Weight

Normal

2 Fat

Normal

B STATURE

Normal

C EXTREMITIES

1 Upper

Normal

a Hands

Normal

b Fingers

Normal

c Span

Normal

2 Lower

Normal

a Feet

Normal

b Toes

Normal

D SPINE

Normal

E INTEGUMENT

1 General

Normal

a Texture

Normal

b Temperature

May rise or fall during attack rectal temperature may rise

c Eruptions

None

d Pigmentation

None

e Color

Variable

2	Hair	Normal, unless associated with adrenal cortical disorder as described below
■	Head	Plentiful, low browed, later recession develops
b	Facial	May be increased in normal places as well as on neck, eyebrows may be thick and heavy
c	Axillary	Normal
d	Pubic	Increased, male distribution may be found in females
e	Body	Normal or increased
F	HEAD	
1	Shape and size	Normal
2	Facial expression	Apprehensive during attack
3	Eyes	
a	General	Normal or possibly slight exophthalmos, pupils dilate during attack. lacrimation may occur ¹¹
b	Fundi	Retinal changes of malignant hypertension may ensue, including choked disks ⁶¹
c	Visual	
(1)	Fields	Normal
(2)	Acuity	May decrease with retinal changes
4	Ears and nose	May have angiospasm and blanching of tip of nose ¹¹
5	Mouth and throat	
a	General	Normal
b	Teeth	Normal
■	Larynx	Normal
G	NECK	
1	General	Normal or distension of neck veins
2	Thyroid	Normal
H	CHEST	Normal or signs of pulmonary edema. respiration may increase during an attack.
I	HEART AND PERIPHERAL VESSELS	
1	Heart	Normal or enlarged and hypertrophied especially the left ventricle, as in hypertension. systolic murmurs
2	Rate and rhythm	Variable but usually increased during paroxysm. irregular or gallop rhythm may be found
3	Blood pressure	Persistent elevation of 20 to 30 per cent above 140/90, ^{1 6 11 13 14 1 7 47 9 63 0} with paroxysmal attacks, systolic may rise above 300 mm and diastolic over 160 mm. ^{11 17 0 1 43 44 57 6 68 69} may have wavelike fluctuations during episodes, none of the attacks lasts less than 10 to 15 min, although symptoms may disappear before the blood pressure returns to its original level. postural hypotension ⁶⁴
4	Peripheral arteries and veins	Pulse variable but during attack very thin and at times not palpable because of intense vasoconstriction. oscillographic recordings may fail to demonstrate any peripheral pulse in severe spells. vessels may be sclerotic. postural tachycardia ⁶⁴
5	Vasomotor	Marked pallor and coldness of face and extremities are usually present in severe attacks. Raynaud's signs have been reported. ⁸ purplish blotching of face and scars may become cyanotic
J	BREASTS	Normal

K. ABDOMEN

- | | |
|----------|-------------------------------------|
| 1 Liver | Normal unless congestive failure |
| 2 Spleen | Normal |
| 3 Hernia | None |
| 4 Tumor | Palpable occasionally ^{6a} |

L. GENITALIA

- | | |
|----------|---|
| 1 Male | May be associated adrenogenital syndrome and secondary sex changes that are found with it |
| 2 Female | |

VII LABORATORY DATA

A. URINE

- | | |
|--------------------|---|
| 1 General | Output decreased and casts may be found during an attack |
| 2 Special analyses | |
| a Sugar | May be found continuously or only during attack ^{10 60 63} |
| b Albumin | Normal or present during an attack |

B. HEMATOLOGY

- | | |
|---------------------|--|
| 1 Red blood cells | Normal |
| 2 Hemoglobin | Normal or decreased |
| 3 White blood cells | Normal or increased |
| 4 Differential | Eosinophilia occasionally ³⁹ rarely eosinopenia ⁴⁰ |

C. BLOOD CHEMICAL ANALYSES

- | | |
|-----------------------|---|
| 1 Sugar | Normal rises during attacks may remain high |
| 2 Nonprotein nitrogen | Normal or increased especially during an attack or post operatively ^{11 60} up to 150 mg % has been reported ⁴¹
As for nonprotein nitrogen ³⁹ |
| a Urea | Normal |
| 3 Protein | Normal or increased |
| 4 Uric acid | Normal or increased ^{6 11 16 48 50 55 63} |
| 5 Cholesterol | Normal or increased ^{11 63} |
| 6 Sodium | Normal ^{11 64} |
| 7 Potassium | Normal or increased rises with an attack ^{11 63} 33.5 mg % has been reported ¹¹ |
| 8 Calcium | Normal |
| 9 Phosphorus | Normal ² |
| 10 Phosphatase | Normal |
| 11 Chlorides | Normal ⁶⁰ |
| 12 Iodine | Normal probably increased during attacks on account of adrenalin effect low total value ^{17 4} |
| 13 Creatine | Normal ³⁸ |
| 14 Creatinine | Normal ⁶ |
| 15 Magnesium | No data |

D. FUNCTION TESTS

- | | |
|--------------------|---|
| 1 Tolerance | |
| a Glucose | Usually normal initial hyperglycemia or may show no rise 50 per cent may be diabetic possibly hypoglycemia after 4 to 6 hrs (or after an attack) (see 103 I J Chart 95 and Table 102 p 1426) ^{10 11 17 26 48 50 64 66} |
| b Glucose insulin | No data may be insulin sensitive |
| c Insulin | No data may be insulin sensitive |
| d Adrenal water | Negative attack precipitated by ingestion of a large quantity of water ^{39 66} |
| 3 Salt deprivation | No data |

2 Hair	Normal, unless associated with adrenal cortical disorder as described below
a Head	Plentiful, low browed, later recession develops
b Facial	May be increased in normal places as well as on neck, eyebrows may be thick and heavy
■ Axillary	Normal
d Pubic	Increased, male distribution may be found in females
e Body	Normal or increased
F HEAD	
1 Shape and size	Normal
2 Facial expression	Apprehensive during attack
3 Eyes	
a General	Normal or possibly slight exophthalmos, pupils dilate during attack lacrimation may occur ¹¹
b Fundi	Retinal changes of malignant hypertension may ensue, including choked disks ⁶¹
c Visual	
(1) Fields	Normal
(2) Acuity	May decrease with retinal changes
4 Ears and nose	May have angiospasm and blanching of tip of nose ¹¹
5 Mouth and throat	
a General	Normal
b Teeth	Normal
■ Larynx	Normal
G NECK	
1 General	Normal or distension of neck veins
2 Thyroid	Normal
H CHEST	Normal or signs of pulmonary edema, respiration may increase during an attack
I HEART AND PERIPHERAL VESSELS	
1 Heart	Normal or enlarged and hypertrophied especially the left ventricle, as in hypertension systolic murmurs
2 Rate and rhythm	Variable but usually increased during paroxysm, irregular or gallop rhythm may be found
3 Blood pressure	Persistent elevation of 20 to 30 per cent above 140/90 ^{1 0} ^{11 12 14 21 3 4 10 6 9} with paroxysmal attacks systolic may rise above 300 mm and diastolic over 160 mm ^{11 17} ^{0 21 43 44 57 60 68 80} may have wavelike fluctuations during episodes none of the attacks lasts less than 10 to 15 min although symptoms may disappear before the blood pressure returns to its original level postural hypotension ⁶⁴
4 Peripheral arteries and veins	Pulse variable but during attack very thin and at times not palpable because of intense vasoconstriction oscillographic recordings may fail to demonstrate any peripheral pulse in severe spells vessels may be sclerotic postural tachycardia ⁶⁴
5 Vasomotor	Marked pallor and coldness of face and extremities are usually present in severe attacks Raynaud's signs have been reported ⁸ purplish blotching face and scars may become cyanotic
J BREASTS	Normal

IX ETIOLOGY

A UNKNOWN

B FAMILIAL TENDENCY¹⁹X PATHOLOGY^{10 11 20}

A GROSS

1 Tumor

a Types

- (1) Benign—largest percentage
- (2) Malignant
- (3) Diffuse hyperplasia
- (4) Aberrant paragangliomas

b Location (see Fig 285)

- (1) More common on right side
- (2) Bilateral
- (3) Aberrant tumors
 - (a) Retroperitoneal area²¹
 - (b) Sacrococcygeal region
 - (c) Along entire course of aorta²²

(d) Carotid body

c Description

- (1) Size—variable
- (2) Encapsulated usually
- (3) Consistency—solid or rather soft and cystic
- (4) Cut surface
 - (a) Pinkish white
 - (b) Bright red
 - (c) Jellylike material
 - (d) Border may be yellow
- (5) Many hemorrhagic areas and extravasation into peritoneum due to increased vascularity
- (6) Necrotic and vacuolar degeneration are as common
- (7) Cortical tissue may be
 - (a) Compressed
 - (b) Hyperplastic

d Metastases to

- (1) Brain
- (2) Neck
- (3) Liver

2 Heart

- a Enlarged
- b Hypertrophied

3 Blood vessels are thickened

B Microscopic

1 Tumor (see Fig 286)

- a Cellular arrangement
 - (1) Alveolar
 - (2) Closely packed
 - (3) Sinusoidal

C Cells

(1) Size and shape are variable, but often

- (a) Large
- (b) Polyhedral (10 to 50 microns)
- (c) Oval or round

(2) Nuclei

- (a) Eccentric or centrally placed
- (b) Oval or round
- (c) Vesicular

(3) Cytoplasm

- (a) Pale
- (b) Granular—adrenalin may be demonstrated by stains¹¹
- (c) Vacuolization often near sinusoids

(4) Few mitoses rarely malignant²³(5) Invasion of blood vessels suggesting possibility of benign metastasizing phenomena as in thyroid tumors¹¹2 Adrenal cortex—hyperplasia if adrenogenital or Cushing's syndrome is also present¹²

3 Thyroid may be replaced by fibrous or lymphoid tissue

4 Pancreas—hyperplasia of islets of Langerhans¹¹

5 Blood vessels

- a Muscularis coat may increase
- b Internal elastic lamina may be¹¹
 - (1) Thickened
 - (2) Ruptured

c Lumina narrowed

d Arterioles may reveal widespread necrosis¹²

6 Kidneys

- a Thickening of glomerular capillaries
- b Fibrosed Bowman's capsules
- c Nephrosclerosis

C CHEMICAL ANALYSES

1 Tumors may contain¹²

- a Epinephrine—to 2 400 mg
- b Nor-epinephrine—53 to 90 per cent²⁴

2 Absence of^{27 28}

- a Fat
- b Lipoids
- c Iron

3 Chromic salts turn tissues brown hence the name chromaffin

4	Balance	
a	Nitrogen	No data
5	Renal	
a	Phenolsulfonphthalein	Normal ⁶³
b	Urea clearance	Variable ^{11 35}
E	MISCELLANEOUS TESTS	
1	Basal metabolic rate	May be increased in continuously secreting tumors or during an attack. (see Chart 96) ^{6 8 10 12}
2	Circulation time	No data but should be increased
3	Sedimentation rate	Normal ¹¹
4	Specific dynamic action of protein	No data
5	Gastric analysis	Normal or decreased ³⁹
6	Electrocardiogram	May change during an attack with S T elevation or depression, T and P waves high, various other abnormalities as found in hypertensive cases, i.e., left ventricular strain patterns ^{11 47 68}
7	Total base	Normal ⁴⁵
F	URINARY HORMONE ASSAYS	
1	FSH	Normal probably ⁴⁰
2	LH	No data
3	Estrogens	Normal probably ⁴⁰
4	Pregnandiol	No data
5	17 ketosteroids	Normal, ⁶⁹ may increase after an attack ⁴
6	11 oxysteroids	Normal ^{11 69} or slight increase ⁴⁰
7	Aschheim Zondek	Negative ¹⁰
8	TSH	No data
9	Epinephrine (or nor epinephrine)	Increased ²² normal or increased in the blood especially during attacks ^{6 60}
G	BIOPSY	
1	Endometrial	No data, but normal probably
2	Testicular	No data but normal probably
H	VAGINAL SMELAR	Normal
I	SEMEN ANALYSIS	Normal

VIII ROENTGENOGRAPHIC FINDINGS

A	SKULL	Negative ¹¹
B	EPIPHYSAL STATUS (bone age)	Normal unless associated with adrenocortical disorders
C	LONG BONES	Normal
D	VERTEBRAE	Normal
E	BONE TEXTURE	Normal
F	MISCELLANEOUS	Tumor may be large enough for demonstration by pyelograms perirenal insufflation or flat plate of abdomen calcified in some rarely shown in chest ⁴⁹ 12 per cent of tumors outside adrenal area (see Fig 284) ⁴⁹

- h Pain
 (1) Epigastric¹⁶
 (2) Precordial
 i Salivation may be excessive
 j Nausea
 k Vomiting
 l Diarrhea
 m Frequency
 n Anuria
 o Facial
 (1) Pallor
 (2) Flushing with circumoral pallor
 p Sweating
 q Tremors of
 (1) Extremities
 (2) Head
 r Leg cramps
 s Tinnitus
 t Mydriasis
 4 Symptoms following attack
 a None may feel well
 b Lassitude
 c Weakness
 d Prostration
- B CHRONIC (when persistent hypertension is present)
 1 Exacerbations may occur as described under acute paroxysms
 2 Symptoms associated with chronic hypertension
 a Cerebral episodes
 b Renal failure
 c Paroxysmal dyspnea
 d Angina of
 (1) Effort
 (2) Decubitus
 3 Weight loss
 4 Diabetes mellitus symptoms (if present)
- C FREQUENCY DURATION AND TIME OF ATTACKS^{12 13 20 29 42}
 1 Frequency
 a Paroxysms eventually increase in number but years may pass between them
 b Irregular intervals
 c Death may occur with first attack
 2 Duration
 a Dependent on amount and duration of epinephrine secretion
 b Range—12 to 16 hrs
 c It is hardly conceivable that the elevation of blood pressure would be less than 4 to 5 min although symptoms may last less than a minute
 3 Time—any hour but more often during day
 4 Pregnancy—attacks may be abated⁴²
- XIII DIAGNOSIS^{1 2 3 8 9 10 11 16 21 22}
^{43 47 49 53 55 63}
- A HISTORY—Paroxysmal episodes consistent with release of excess epinephrine
- II SYMPTOMATOLOGY
 1 Dizziness
 2 Headache
 3 Sweating
 4 Substernal pain
 5 Dyspnea
 6 Tremor
 7 Nausea
 8 Vomiting
- C PHYSICAL STATUS
 1 Blood pressure
 a Fluctuates
 b Remains elevated
 c Increases during paroxysms
 2 Palpable tumor in either upper abdominal quadrant
 3 Fundi may show retinal changes of hypertension
 4 Signs of adrenocortical disturbance are rare
- D LABORATORY DATA
 1 Increase in
 a Nonprotein nitrogen (blood)
 b Urea (blood)
 c Potassium (serum) especially during attacks
 d Epinephrine (blood)
 e Basal metabolic rate
 2 Perirenal insufflation by presacral route
- E SPECIAL TESTS (for methods see 39 \ VIII C 4)^{29 31}
 1 Repetition of acts which have been thought to incite a paroxysm or hypertension
 2 Massage of tumor produces a paroxysm
 3 Induction of paroxysm of hypertension by
 a. Adrenalin
 b. Histamine
 c. Etamon
 d. Mecholyl

XI PATHOLOGIC PHYSIOLOGY

A GENERAL

- 1 The initial abnormal changes which occur in the body from a chromophil tissue tumor are entirely due to an excess of circulating epinephrine and/or nor epinephrine
- 2 All symptoms or signs observed in a typical paroxysmal attack have been noted from an excess administration of the epinephrine in either animals or man (see also 39 VI B 2)
- 3 It seems likely that stimulation of sympathetic nerves ending in the tumor cause discharge of accumulated epinephrine within the cells
- 4 In cases with persistent elevation of blood pressure, a vicious circle suggests itself
 - a The continuous excess of epinephrine stimulates the sympathetics which, in turn, cause the tumor cells to discharge their hormone
 - b It is doubtful if the mechanism is as simple
- 5 The occurrence of diabetes* 30
 - a Its cure following removal of the tumor suggests the possible elaboration of carbohydrate hormones by the cortex
 - b Epinephrine may cause release of adrenocorticotropin which in turn stimulates the cortical hormones
 - c The increased bodily metabolism due to excess epinephrine as well as its action on the whole carbohydrate mechanism may indicate the exacerbation of a latent diabetes in some cases
- 6 Death from an excess of epinephrine or nor epinephrine in man may be similar to that in animals³¹
 - a Excitement followed by depression
 - b Heart rate is very rapid
 - c Respirations—increased
 - d Muscular paralysis may develop
 - e Asphyxial convulsions
 - f Multiple hemorrhages throughout the body
 - g Cardiac dilatation
 - h Pulmonary edema due to left heart failure

XII SYMPTOMATOLOGY

A ACUTE

- 1 No complaints in 11 per cent of cases¹¹
- 2 Precipitating factors—discoverable in 50 per cent may occur during sleep
 - a Pain
 - b Exercise
 - c Hyperventilation
 - d Emotion
 - e Sneezing
 - f Excess intake of
 - (1) Food
 - (2) Fluids
 - g Position
 - (1) Lying on side of tumor
 - (2) Bending forward or backward
 - h Labor
 - i Menses
 - j Carotid sinus pressure⁴⁰
 - k Anesthesia⁴
 - l Surgical operations
 - m Tumor, direct
 - (1) Palpation
 - (2) Massage
 - n Cold pressor test (see 39 VIII C 4 c)
 - o Injection of (see 39 VIII C 4 a, b)
 - (1) Histamine⁴²
 - (2) Mecholyl
 - (3) Etamon⁴⁶
 - (4) Adrenalin (1 to 2 mg) (may be hyposensitive)^{8 19 47 50 51}
 - (5) Cocaine
- 3 Symptoms during paroxysm
 - a Peculiar feelings that are difficult for patient to describe and which might be considered functional i.e. an anxiety state or neurosis
 - (1) Sinking sensation in abdomen
 - (2) Apprehension often severe
 - (3) Dizziness
 - (4) Choking
 - b Headache
 - (1) Pounding
 - (2) Expanding
 - c Breathing
 - (1) Dyspnea
 - (2) Hyperventilation with tetany
 - d Palpitations
 - e Chest
 - (1) Pressure
 - (2) Constriction
 - f Cough
 - g Hemoptysis

- 2 Cushing's syndrome^{17 40}
- 3 Diabetes mellitus^{9 30}
- 4 Neurofibromatosis⁶⁰
- 5 Tuberculosis

XVI TREATMENT

A SURGICAL

- 1 Operative removal of tumor²⁸
- 2 Anti epinephrine drugs for prevention of operative hypertensive crisis^{7 33}
 - a Technique—see 39 \III C 4 a b
 - b Test should be done before surgery to learn effect and tolerance of drug
 - c Intravenous apparatus should be ready at the beginning of the operation
 - d Solution is started if pulse rate and blood pressure rise rapidly
 - e Amount given depends on the effect and tolerance on previous test
 - f Great caution should be used for too much of the medication might depress the blood pressure to fatal levels (see Chart 97)
- 3 Preoperative and postoperative therapy—see 40 \VI A 42 \VI

B GENERAL

- 1 For symptomatic relief of paroxysmal attacks
 - a Amyl nitrite inhalations^{43 43 43}
 - b Pressure on eyeballs⁴³
 - c Morphine may be helpful
 - d Dioxobenzene²⁹
 - e Dibenzamine
 - f Venesection⁴⁷
 - g Lumbar puncture for severe headache⁴⁷

- 2 Other complaints—management as required

XVII PROGNOSIS

A UNTREATED CASES

- 1 Almost normal life span if attacks are infrequent
- 2 Outlook is poor when paroxysms increase in
 - a Length
 - b Severity
- 3 Unfavorable prognosis with sustained attacks and severe hypertension

B OPERATED CASES

- 1 Outlook is excellent if patient survives operation
- 2 Removal of benign tumor may be followed by a malignant growth on the other side[—]
- 3 Mortality^{10 34 41 42 47}
 - a To date—22 per cent
 - b Since 1944—around 10 per cent
- 4 Diabetes mellitus may be
 - a Cured²⁰
 - b Ameliorated
- 5 Hypertension (probably unrelated to tumor) to some degree may persist although paroxysms disappear

XVIII CAUSES OF DEATH

A CARDIAC FAILURE³

B CEREBRAL ACCIDENTS

C UREMIA

D POSTOPERATIVE ACUTE ADRENAL INSUFFICIENCY

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- 4 Prevention of induction of paroxysmal hypertension by preliminary use of
 - a Dioxobenzane
 - b Dibenamine
- 5 Lowering or return of persistently elevated blood pressure by^{17 4 67}
 - a Dioxobenzane
 - b Dibenamine

XIV DIFFERENTIAL DIAGNOSIS

A ESSENTIAL HYPERTENSION (including malignant type)

- 1 History is important, often asymptomatic
- 2 Differentiation from pheochromocytoma with persistent hypertension may be difficult
- 3 Epinephrine excess is not demonstrated in blood
- 4 Adrenal tumor is not found on roentgen films, but this does not exclude pheochromocytoma

B NEUROSES

- 1 Chronically not well
- 2 Attacks of nervousness and associated symptoms are not as severe
- 3 Blood pressure within normal variations
- 4 Blood chemical analyses—normal

C PAROXYSMAL TACHYCARDIA

- 1 Tachycardia is sudden in
 - a Onset
 - b Cessation
- 2 Heart rate—more rapid
- 3 Blood pressure
 - a Fluctuates
 - b Is not so high
 - c Should be taken during questionable attacks to exclude
 - (1) Paroxysmal hypertension
 - (2) Pheochromocytoma

D HYPERTHYROIDISM (see 26 VI)

- 1 History
 - a Appetite increased
 - b Weight loss
 - c Chronic fatigue
- 2 Thyroid enlargement
- 3 Diastolic pressure low
- 4 Peripheral vasodilatation
- 5 Cholesterol (plasma) is decreased
- 6 Basal metabolic rate is higher by average

E HYPOLYCEMIC ATTACKS

- 1 Occurrence in relationship to meals

- a Hypoglycemia—several hours later
- b Pheochromocytoma—immediately

2 Blood sugar

- a Hypoglycemia—low, 50 mg % or less
- b Pheochromocytoma
 - (1) Normal
 - (2) Increased

3 Potassium (serum)—not elevated

F CUSHING'S SYNDROME WITH HYPERTENSION

- 1 Characteristic body changes
- 2 Paroxysms absent
- 3 Blood pressure unchanged by
 - a Dibenamine
 - b Dioxobenzane

G ANGINA PECTORIS AND CORONARY OCCLUSION

- 1 Past history may be helpful
- 2 Hypertension
 - a Absent in some cases
 - b When present, exclusion of pheochromocytoma may be
 - (1) Difficult
 - (2) Impossible

XV COMPLICATIONS SEQUELAE AND ASSOCIATED DISEASES

A COMPLICATIONS

- 1 Cerebral vascular accidents due to increased intracranial pressure
- 2 Angina pectoris
- 3 Coronary occlusion
- 4 Cardiac failure
 - a Acute left ventricular
 - b Chronic congestive
- 5 Pulmonary edema
- 6 Chronic vascular nephritis
- 7 Retinitis
- 8 Intraperitoneal hemorrhage from tumor¹⁸
- 9 Metastases
- 10 Toxemia of pregnancy

B SEQUELAE

- 1 Postoperative adrenal insufficiency because of inactive adrenal on opposite side
- 2 Others as listed above

C ASSOCIATED DISEASES

- 1 Adrenal cortical
 - a Hypofunction (with malignant tumor)²²
 - b Hyperfunction²⁴

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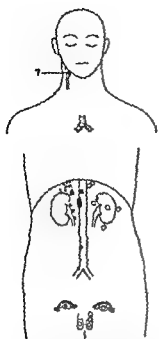


FIG 285 VARIOUS LOCATIONS OF ABERRANT ADRENAL MEDULLARY TISSUE OR PHEOCHROMOCYTOMA

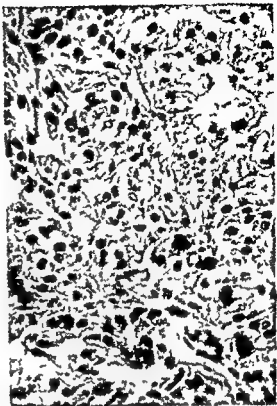


FIG 286 MICROSCOPIC APPEARANCE OF PHEOCHROMOCYTOMA

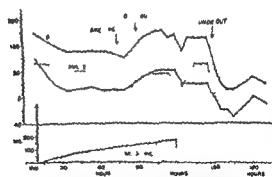


CHART 97 USE OF DIBENAMINE PRE OPERATIVELY IN CASE OF PHEOCHROMOCYTOMA Note the gradual and cautious introduction of dibenamine. The use in this case is inconclusive yet the rise in pressure on removal of tumor is less than would ordinarily be expected (Barte's E C, and Cat ted R Pheochromocytoma its diagnosis and treatment Ann Surg 131 903 916)

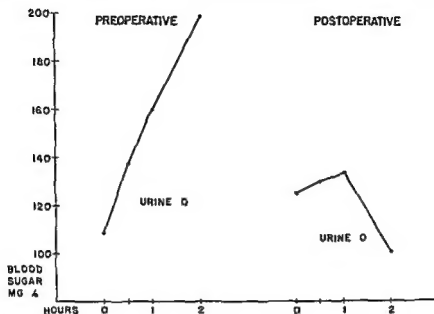


CHART 95 GLUCOSE TOLERANCE CURVES IN PHEOCHROMOCYTOMA (*Left*) Before operation for removal of tumor (*Right*) One week later (Bartels E C and Arnold W T Essential features for the diagnosis of pheochromocytoma, report of a case Labey Clin Bull 6 132 142)

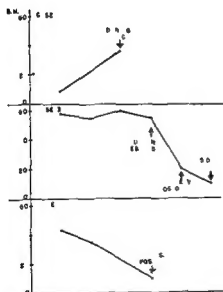


CHART 96 BASAL METABOLIC RATE IN PHEOCHROMOCYTOMAS (3 cases) (*Top*) Before and during paroxysmal hypertension (*Center*) Before and immediately after removal of tumor in a case with persistent hypertension (*Bottom*) Another case with persistent hypertension in which BMR was taken preoperatively and 2 months afterwards (Bartels E C and Cattell R B Pheochromocytoma its diagnosis and treatment Ann Surg 131 903 916)



FIG 284 ROENTGENOGRAM SHOWING CALCIFICATION IN PHEOCHROMOCYTOMA (See also Charts 95 and 96 center) Multiple extra adrenal tumors were found at operation

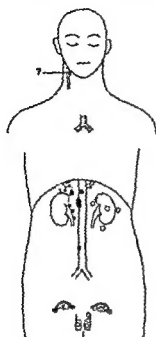


FIG 285 VARIOUS LOCATIONS OF ABERRANT ADRENAL MEDULLARY TISSUE OR PHEOCHROMOCYTOMA

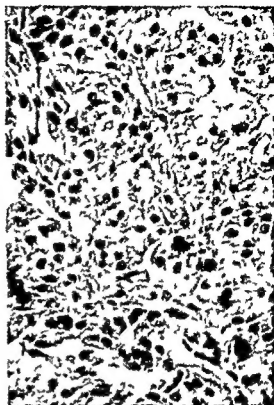


FIG 286 MICROSCOPIC APPEARANCE OF PHEOCHROMOCYTOMA

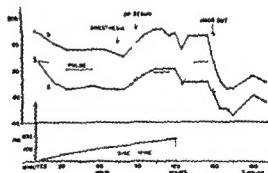


CHART 97 USE OF DIBENAMINE PREOPERATIVELY IN CASE OF PHEOCHROMOCYTOMA. Note the gradual and cautious introduction of dibenamine. The use in this case is inconclusive yet the rise in pressure on removal of tumor is less than would ordinarily be expected. (Partell E C and Catell R. Pheochromocytoma: its diagnosis and treatment, *Ann Surg* 131 903-916)

